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PREFACE

The Editorial Committee and editors wish to express deep gratitude to our authors, who so willingly have shared their funds of knowledge with the readers of *Annual Review of Medicine*. We also wish to thank the subscribers who gave constructive criticism, and we take pleasure in the wide acceptance of this *Review* by those in search of authoritative surveys of medical progress. The editors gratefully acknowledge, too, the valuable aid of Miss Beryl Daniel, Editorial Assistant.

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INFECTIOUS DISEASES (BACTERIAL)

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and

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Introduction

In recent years the interest of many investigators has gradually shifted toward the isolation, identification, and understanding of the causative agents of diseases resulting from microorganisms smaller than bacteria. Nevertheless, many fundamental and clinical problems associated with bacterial infections remain unsolved. While there is some difference of opinion as to whether staphylococci actually produce more serious infections than previously, it is generally agreed that infections caused by the staphylococcus continue to be a difficult therapeutic challenge. Evidences of bacterial infections of the kidney are found in approximately one-third of patients coming to autopsy. Pyelonephritis is, in all probability, the most common serious disease today for which there is the greatest immediate potential for prevention and treatment. The mortality rates of pneumococcal meningitis and tetanus remain high——to mention a few of the problems. It is the purpose of this review to summarize briefly some of the contributions made during the year ending July 1, 1957, to the understanding of the pathogenesis and management of bacterial infections.

Staphylococcal Infection

A conference on staphylococcal infections was held at the New York Academy of Science in February of 1956. The papers presented at this conference have been published in the *Annals of the New York Academy of Science* (1). Excellent reviews of the clinical aspects of the problem were given by McDermott (2), Spink (3), Finland & Jones (4), Knight *et al.* (5), and Collins *et al.* (6). Subsequently, an excellent discussion of the subject has been published by Rogers (7).

Staphylococcal infections continue to be a serious problem in hospitalized patients. It seems most likely that these infections have not actually increased in frequency but that there is an increase in the number of susceptible patients in hospitals. Among these patients infections are often more severe. At any rate, staphylococcal infections contracted by patients after hospital admission are likely to be more difficult to treat because of the elimination of the antibiotic-sensitive strains by the widespread use of these drugs within the hospital. The meager success in handling staphylococcal septicemia is illustrated by the experience at the Cincinnati General Hospital (8).

During the past 15 years, 55 cases of established blood stream infection were seen, 35 of which had acute bacterial endocarditis. Thirty-nine of the 55 patients died. During the seven-year interval between 1940 and 1947 when the sulfonamides, penicillin, and streptomycin were used, 83 per cent of the patients died, and since 1948, 62 per cent have died. Before 1948 87 per cent of the patients with endocarditis died and since 1948, 60 per cent died. Acute endocarditis is one of the most serious forms of staphylococcal infection and the presence of meningitis, cerebritis, and petechial hemorrhages of the skin almost always means the development of this complication. Successful management depends on prolonged high dose chemotherapy guided by *in vitro* antibiotic testing. Levin (9) reported an outbreak of staphylococcal infection occurring on the Surgical Service of Manchester, New Hampshire, Veterans Hospital. From December of 1955 through February of 1956 there were 17 cases of staphylococcal infection. These included three cases of pyogenic parotitis with one death. Many authors (3, 9, 10) have emphasized the need for elimination of cross contamination from patient to patient, aseptic techniques in handling wound dressings, and elimination of hospital carriers. Studies of the incidence of staphylococcal carriers in most hospitals have revealed the number to be quite high. Loh & Street (11) reported that among 100 hospital personnel who worked on a maternity ward of a 304-bed community hospital, 34 per cent were found to be staphylococcal carriers; 19 per cent were nasal carriers, 6 per cent pharyngeal, and nine per cent nasopharyngeal. Antibiotic sensitivity studies of the 43 strains of staphylococci isolated revealed that nine were resistant to penicillin, seven to oxytetracycline, seven to tetracycline, six to streptomycin, none to erythromycin and chloramphenicol. In contrast to this experience, most other studies have revealed a higher incidence of penicillin, tetracycline, and streptomycin resistance among strains isolated from hospital patients and personnel.

A report by Hartmann & Angevine (12) on 17 cases of pseudomembranous colitis, complicating prolonged antibiotic therapy, revealed that *Staphylococcus aureus* was isolated in some cases but absent in others. This is consistent with the opinion of others (13) that the staphylococcus is just one form of superimposed infection of the bowel but that other forms of pseudomembranous colitis occur.

Because of the incidence of strains of staphylococci resistant to the usually administered antibiotics, the search has continued for the agents active against these resistant strains. Among the antibiotics recently studied are included novobiocin, vancomycin, and ristocetin. Rutenburg, Shapiro & Schweinburg (14) reported on the use of novobiocin in the treatment of surgical infections caused by staphylococci and other Gram-positive bacteria. Most strains were inhibited by concentrations less than 6.25 μg./ml., but 2 out of 40 were resistant to concentrations greater than 50 μg./ml. The experience in the treatment of staphylococcal infections was generally good at a dosage of 250 mg. every 6 hr. Two of the 90 patients

had mild gastrointestinal side effects. There have been reports indicating a higher incidence of skin rashes in association with novobiocin therapy if doses in a range of 2 to 3 gm. daily are given.

In experimentally produced staphylococcal infections in mice, Smith (15) observed certain similarities to human infections. In experimental infections the organisms were found to survive best in the lungs and kidneys. This corresponded with human autopsy findings in 22 autopsied patients. In mice the virulence of the staphylococci was related to their ability to multiply in the mouse kidney, and in human infection the prognosis was related to the formations of abscesses in the kidney parenchyma. Further studies of infections in mice by Rogers & Melly (16) have shown that virtually all of the staphylococci in the blood stream are found within the circulating polymorphonuclear leukocytes within 10 to 40 min. after injection of the culture. There is an initial marked drop in the granulocytes in the circulating blood but by the end of 40 min. they return to the circulation in large numbers. Apparently trapping occurs initially in the pulmonary vascular bed and less constantly in the splanchnic viscera. These findings suggest the staphylococci are phagocytized by the polymorphonuclear leukocytes temporarily sequestered in the lungs and splanchnic viscera. It appears that the same sequestered polymorphonuclear leukocytes containing viable staphylococci subsequently return to the circulation. Such intraleukocytic organisms are believed to play a role in the maintenance of the bacteremia. Similar studies using *Escherichia coli* have revealed that there was a prolonged granulocytopenia following the injection of this organism and the bacteria were rapidly killed following ingestion by the polymorphonuclear leukocytes (17).

In an attempt to avoid some of the errors inherent in the production of experimental staphylococcal infections in animals, Elek (18) produced infections in the skin of man. He found that there was no significant difference in the virulence of known pyogenic strains and those from nasal carriers as measured by pus formation. He also confirmed the previous observation that the presence of foreign bodies interferes with the local defense against staphylococcal infections. E. T. Bynoe, in commenting on this paper, quoted from the experience of Barber & Burston (19) in which there seemed to be considerable difference in the virulence of strains isolated from carriers and from abscesses. Organisms transmitted from nursery employees to babies rarely caused severe infection, but when a nurse entered the nursery with a boil on her face, several severe infections occurred. One must still take into consideration the dose of infecting organisms when evaluating virulence.

While the staphylococcus shows many interesting biologic properties, Lack (20) believes there is little evidence that these have any relationship to pathogenicity. Even the much used coagulase test is of little value in separating pathogenic and nonpathogenic strains although there is some association between coagulase production and resistance to neutrophil

lysozyme. Ekstedt (21) showed a close correlation between coagulase production and the ability of the strain to grow well in normal undiluted human serum. He felt that there was little evidence of a direct correlation between either of these properties and pathogenicity. According to Rammelkamp & Lebovitz (22), the evaluation of the role of coagulase in staphylococcal infections is further complicated by the fact that most adults have a fairly high titer of reacting factor in serum which interferes with the evaluation of the coagulase reacting factor system in human infection. They suggest that studies in children might clarify the role of this system since the titer of reacting factor is rarely elevated in young age groups. Relative to this same problem Fishman & Silverman (23) isolated from the polymorphonuclear leukocytes by ultrasonic technique a substance from the mitochondrial section of the cells which has a bactericidal effect against many bacteria. As little as 0.31 μg. of nitrogen-containing material was capable of killing 2,000 cells of *Micrococcus pyogenes*. This substance was differentiated from lysozyme by its heat stability, ultraviolet spectrum and enzymatic inactivation, and in having a wider antibacterial spectrum of activity.

Wise (24) has cultured small colonies (G variants) of staphylococci from patients. These variants were more resistant to antibiotics than the parent strain. They were avirulent but remained viable in animal tissues without producing infection. When they are subcultured in nutrient broth they revert to large colonies. It is suggested that these variants may persist in human tissue during and following antibiotic therapy and serve a subsequent source of relapse or recurrent infection.

The staphylococcal enterotoxin has been purified and its properties described by Bergdoll (25). Satisfactory assay procedures have not been developed.

Bacterial Infections of the Urinary Tract

There is evidence of increasing awareness of the tremendous problem of bacterial infections of the urinary tract as manifested by the increase in number of papers appearing on various aspects of this subject during the past year. An excellent review by Derow (26) summarizes the present concepts of the pathogenesis and treatment of pyelonephritis.

The understanding of many aspects of this disease has been delayed by difficulties in the production of the disease experimentally in animals. Braude, Shapiro & Siemiensky (27, 28) reported two years ago of the production of hematogenous pyelonephritis in rats. This was done by massaging the kidney and injecting cultures of the *E. coli* intravenously. It is well known that urinary tract infections are often associated with obstruction of the ureter. Guze & Beeson (29) have attempted to elucidate the mechanism by which obstruction affects the susceptibility of the kidney to infection. The ureter in rats was ligated and *E. coli* or *Serratia marcescens* injected intravenously. During the first few hours following the injection,

approximately equal numbers of bacteria could be recovered from the kidney on the obstructed side as compared to that on the unobstructed side. After 4 hr., however, an increased number of bacteria could be demonstrated on the obstructed side, apparently the result of multiplication, and by the end of 24 hr. purulent infection was usually present. It was concluded that the increased susceptibility of the obstructed kidney to infection introduced by way of the blood stream was not attributable to an increased trapping of circulating bacteria.

A study by Kass & Schneiderman (30) demonstrated that bacteria may enter the bladder in patients having indwelling catheters, even though the interior of the catheter is not contaminated. A small amount of a culture of *S. marcescens* was applied to the periurethral epithelium of one female and two male patients with inlying catheters. Within one to three days large numbers of the test organisms were recovered from the urine of these patients. It was suggested that the entry was by way of the fluid composed of urine and exudate that usually forms around the catheter.

It is often difficult to evaluate the significance of positive urine cultures. In an attempt to shed some light on this problem, MacDonald *et al.* (31) studied the relationship between pyelonephritis and bacterial counts of the urine. Bacterial counts of bladder urine were performed in 100 unselected autopsies and these findings were correlated with the results of pathologic study of the kidneys. Forty per cent of the urine specimens obtained at autopsy by needle aspiration of the bladder contained more than 100,000 bacteria per ml., 53 per cent contained no bacteria, and 7 per cent contained between 10 and 10,000 organisms per ml. Histologic evidence of active pyelonephritis was found in 14 of the 40 patients with greater than 100,000 bacteria per ml. and occurred in only 3 of the 60 patients with no or relatively few bacteria. In three cases of acute cystitis there were more than 100,000 bacteria per ml. The organism isolated most frequently was *Aerobacter aerogenes* and the review of the cultures taken prior to death revealed little tendency of the organism to disappear with treatment. Antimicrobial therapy had been given up to at least 24 hr. before death in 60 to 70 per cent of the patients but beneficial effects of such therapy were limited. Healed pyelonephritis occurred in 18 per cent of the patients and the prevalence bore no relationship to bacteriuria. Thirty-three per cent of unselected autopsies revealed evidence of active or healed pyelonephritis. Substantial correlation between the bacteriuria, pyelonephritis, and inlying catheterizations was demonstrated. The clinical diagnosis of active infection of the genitourinary tract was not made in 70 per cent of the cases in which active pyelonephritis was demonstrated histologically. In many of these patients, extensive pyelonephritis was found at autopsy. The authors stated that pyuria, azotemia, cylindruria, and albuminuria were not reliable indices of the presence or absence of bacteriuria or pyelonephritis and they found little or no relationship between hypertensive heart disease, increased diastolic pressure, and the bacteriuria found.

Guze & Beeson (32) reported observations on the reliability and safety of bladder catheterizations for bacteriologic study of the urine. Urine cultures were taken on 13 women after careful cleansing of the genitalia and urethra just prior to undergoing gynecologic surgery. After the catheter was inserted into the urethra it was swirled in sterile saline; 2 ml. of this were cultured in thioglycollate broth and pour plates were made of the saline. There was growth in six cases: *E. coli* was isolated in four, *E. coli* and staphylococcus in one, and *A. aerogenes* in one. However, the pour plates revealed that the colony count was less than 100 per ml. in each case, suggesting that the bacteria could have been introduced by the catheter as it passed through the urethra. In 12 patients, bladder urine was obtained by needle aspiration through the bladder wall during a laparotomy. This urine was compared with specimens obtained by catheterization shortly afterward. In eight of the patients both samples showed no growth. In four, the urine from the bladder was sterile, but the catheterized urine obtained a few minutes later showed *E.* coli in three, *Pseudomonas aeruginosa* in one, and the pour plate from one patient showed only three colonies per ml. In one of the twelve patients, an acute urinary tract infection developed clinically 36 hr. after catheterization. These authors concluded that a clean voided specimen inoculated on solid media was the preferable method of obtaining a urine culture.

Studies by Berg, Weinberger & Dienes (33) suggest the possibility that pleuropneumonia-like organisms may be important in the pathogenesis of unexplained genitourinary infections. Of 88 patients with unexplained genitourinary infections, 57 had positive cultures of pleuropneumonia-like organisms. Most of the 57 symptomatic patients with positive cultures had symptoms suggestive of urethritis. Fourteen of them had arthralgias and eight of the patients had conjunctivitis.

The importance of pyelonephriits in pregnancy, often masquerading as toxemia of pregnancy, was reviewed by Finnerty (34). Of 1130 patients referred to the toxemia clinic at the District of Columbia General Hospital, 73 were found to have pyelonephritis. None of these had any urinary tract symptoms, fever, or costovertebral angle tenderness. The diagnosis was made by microscopic urinalysis and urine culture. Thirty-seven were antepartum, referred because of toxemia and 36 were postpartum, referred because of persistent albuminuria. *E. coli* was cultured in 41, *E. intermedius* in seven, *Proteus* in five, *A. aerogenes* in three, *P. aeruginosa* in three, *Micrococcus* in three, and paracolon bacteria in one.

An excellent review of the pathogenesis, course and treatment of nonobstructive pyelonephritis was reported by Brainerd & Cecil (35).

Bacterial Endotoxins

Interest has continued in the relationship between bacterial endotoxins and the production of certain physiologic changes associated with bacterial disease. Differences of opinion still exist regarding the relative importance

of the meningococcal endotoxin and insufficiency of the adrenal cortex in the production of peripheral circulatory collapse in fulminating meningococcemia. A paper by Kanter & Learner (36) reported findings in ten recently treated cases of meningococcemia with vascular collapse. Five of these patients died despite antibiotics, sulfonamides, adrenal steroids, and norepinephrine. Three died in the first 24 hr., and at autopsy all had massive adrenal hemorrhage. One died in 48 hr. with an acute myocarditis and congestive heart failure, and one died in seven days with extensive cerebral, cardiovascular, renal, and adrenal damage. Of the five who survived, two had slow convalescence because of acute myocarditis but none had evidence of chronic adrenal insufficiency as measured by urinary 17-ketosteroid excretion and by circulating eosinophil counts.

In studies of the role of epinephrine in reactions produced by endotoxins of Gram-negative bacteria, Thomas (37) produced extensive lesions of dermal hemorrhagic necrosis in rabbits by injecting epinephrine or norepinephrine into the skin within 4 hr. after intravenous administration of endotoxin. As little as 5 μg. of intradermal epinephrine and 1 μg. of intravenous endotoxin were sufficient. No lesions were produced by a combination of endotoxin with serotonin and vasopressin or ephedrine. These dermal lesions could be prevented by the pretreatment with cortisone, phenoxybenzamine (Dibenzyline), and chlorpromazine, but not by heparin or nitrogen mustard, both of which inhibit the Shwartzman phenomenon. The nitrogen mustard actually increased the size of the lesions. It was concluded that the endotoxin altered the reactivity of blood vessels to epinephrine in such a way that this hormone becomes a potent necrotizing agent. In a second paper on this subject, Zweifach, Nagler & Thomas (38) discuss the changes produced by the endotoxin in the vascular reactivity to epinephrine in the rat mesoappendix and the isolated perfused rabbit ear. Following the intravenous injection of sublethal doses of endotoxin, the terminal arterioles and venules exhibited greatly augmented and prolonged vasoconstrictor responses to epinephrine and norepinephrine. Hyper-reactivity became evident within 30 min. and persisted as long as 6 hr. After large doses, vascular hyper-reactivity to epinephrine was of briefer duration and was followed by marked hyporeactivity. With lethal doses the terminal arterioles and venules became completely refractory to epinephrine while hyper-reactivity persisted in larger arteries and veins. The end result was pooling of blood and distended capillaries and venules accompanied by the appearance of petechiae. Tolerance to endotoxin by repeated small doses eliminated this effect. It was suggested that abnormal reaction to epinephrine and norepinephrine in the tissues of the intact animal may represent the basic mechanism in the intoxicating and tissue-damaging properties of endotoxin.

The mechanism of the protective effect of chlorpromazine against the *Brucella* endotoxin was studied by Abernathy, Halberg & Spink (39). The survival time in both intact and adrenalectomized mice when challenged

with lethal doses of *Brucella* endotoxin was prolonged by treatment with chlorpromazine. This effect did not appear to be critically dependent on corticoid-stimulating, sedative, adrenolytic, antihistaminic, or hypothermic effects of the drug. Weil *et al.* (40), in an attempt to determine the role of the central nervous system in shock, injected endotoxin from *Brucella melitensis* and *E. coli* intravenously into dogs. The characteristic hemodynamic changes associated with arterial hypotension and portal hypertension were measured directly with a strain gauge manometer. Cross cerebral circulation studies showed that both dogs developed the same changes. Arterial hypotension was not prevented by chordotomy with or without vagotomy. In decapitated dogs there was also a prompt fall in arterial blood pressure with a rise of the portal venous pressure. When the entire spinal cord of cats was pithed, endotoxin still caused a profound drop of arterial pressure with a small elevation of portal venous pressure. These findings do not support the thesis that the initial manifestation of shock produced by endotoxin is a result of a direct action on the central nervous system.

On the other hand, Keene (41) reported that when *Shigella* endotoxin was injected intrathecally in the rabbit it was a thousand times as effective in producing fever as when given intravenously. The latent period was 10 to 12 min. shorter than by way of the intravenous route when the same dose was given. Animals tolerant to the intravenous dose did not demonstrate tolerance to the intrathecal dose. There was no significant leukopenia in contrast to that seen following intravenous injection.

In studying the effect of heat on exogenous and endogenous pyrogens in the serum of dogs, Petersdorf & Bennett (42) presented evidence to support the concept that endogenous pyrogen was not a product of injured tissue but represented a modification of endotoxin by plasma components. Further studies (43) by these authors on the pathogenesis of fever revealed that sterile canine peritoneal exudates containing leukocytes were capable of producing fever when injected into normal dogs but were nonpyrogenic in rabbits. The capacity of these fluids to produce fever was destroyed by heating at 90°C. and they did not produce tolerance when repeatedly injected. They were as potent in normal dogs as in dogs with acquired resistance to bacterial endotoxin. Rabbit exudates are nonpyrogenic for dogs. These findings suggest species specificity in activity of the endogenous pyrogens.

A clinical report by Ezzo & Knight (44) of 38 patients with bacterial shock revealed experiences similar to those described by others. Twenty-three of the 38 cases were caused by Gram-negative bacillary infections and 14 by Gram-positive cocci. The usual portal of entry was the genitourinary tract. The authors were impressed by the relationship between the inflammatory reaction at the portal of entry and the severity of the bacterial shock and ultimate mortality. The use of vasopressors, antibiotics, and corticoids resulted in recovery in 13 cases. The precise value of each in a therapeutic regimen was difficult to determine.

The role of endotoxin in the susceptibility of animals to bacterial infections was studied by DuBos & Schaedler (45). Mice were injected intraperitoneally with one of the endotoxic active products, either pertussis vaccine, heat killed *Klebsiella pneumoniae,* or *Salmonella typhosa* purified lipopolysaccharide. Animals were then given intravenously virulent cultures of coagulase-positive staphylococci, organisms of bovine tuberculosis, or Friedlander's bacilli. A comparison was made of mortality rates in the control and treated groups. Mice receiving infected cultures within a few hours of endotoxin were more susceptible than normals. In contrast, those infected several days after receiving endotoxin were more resistant than normal. The same authors (46) studied changes in susceptibility to infections brought about by nutritional disturbances. In guinea pigs the intradermal injection of 2 μg. of epinephrine lowered the resistance to infection by *Pseudomonas, Proteus, E. coli, S. aureus, C. diphtheriae, Streptococcus hemolyticus,* and *Clostridium welchii,* if the bacteria were injected within 2 hr. at the same site. Mice fed deficient diets were shown to have decreased resistance to infection as manifested by increased mortality. However, they progressively recovered normal resistance while being kept on the same inadequate diet. Susceptibility seemed to increase during periods when animals were losing weight regardless of the cause of the weight loss. These changes were reversible and could occur within short periods of time. This was not thought to be correlated with the properdin level.

The injection of lipopolysaccharide in mice, on the other hand, caused a rapid rise in the resistance to infection, accompanied by a rise in properdin titer to levels of two to three times normal (47). Control animals infected with Gram-negative organisms showed progressive decline in properdin levels and ulitmately the animals died. Those treated with the lipopolysaccharide maintained a normal or increased properdin level and the infection was successfully managed.

Infections Complicating Antibiotic and Steroid Therapy

There is an increasing experience in the association of both fungal and bacterial infections seen in association with antibiotic and steroid therapy. Torack (48) reported eight cases of monilial infection, two of *Aspergillus* and three of *Mucor.* Smith & Cleve (49) describe six cases of severe infection with three deaths occurring in patients receiving steroid therapy. One had a disseminated monilial infection, one a disseminated histoplasmosis, one a staphylococcal septicemia and acute endocarditis, and two had large gluteal abscesses.

Brucellosis

Three cases of chronic localized pulmonary brucellosis were reported by Weed, Sloss & Clagett (50). There were solitary pulmonary lesions found to be caseous granulomas when surgically excised. *Brucella suis* was isolated from each of these. Additional cases of unusual forms of brucel-

losis have been reported: one in the case records of the Massachusetts General Hospital (51) in which there were localized granulomata of the spleen with focal calcifications in association with a hemolytic anemia. A similar case was reported from the Mayo Clinic by Osmuadson, Martin & Stroebel (52) of an individual who had had evidence of the disease for 14 years. Massive splenomegaly, thrombocytopenia with calcified granulomas in the spleen and liver were present. *B. suis* was cultured from this patient. Recently Spink (53) has reported a similar case.

Bacterial Endocarditis

As operations have been performed more frequently on the heart and vessels, the occurrence of postoperative endocarditis has been observed with increased frequency. A case is reported in which cardiac catheterization and mitral commissurotomy were followed by endocarditis caused by *Staphylococcus albus* which was highly resistant to penicillin (54). The patient recovered with combined erythromycin and streptomycin therapy. Geraci (55) has reported further experiences with short-term therapy of combined penicillin and streptomycin for bacterial endocarditis caused by penicillin-sensitive streptococci. He reported an additional 23 cases of a total of 46, with no treatment failures or relapses. Patients in the earlier group were given 2,000,000 units of aqueous procaine penicillin and 2 gm. of streptomycin, divided in two doses and given at 12 hr. intervals. All strains in this group except one were sensitive to 0.1 units of penicillin per ml. *in vitro,* one being sensitive to 0.2 units. In the 23 patients treated subsequently there were six strains sensitive to penicillin concentrations of between 0.1 and 0.5 units. All patients were treated for two weeks. The treatment of staphylococcal endocarditis is reviewed by Melton & Logue (56). Six cases of subacute staphylococcal endocarditis are reported with cures in all but one. The successful therapy in this group illustrates the tremendous difference in prognosis in subacute staphylococcal endocarditis as compared to acute staphylococcal endocarditis. Austrian (57) reported observations on six cases of pneumococcal endocarditis. All of these patients except one had an associated meningitis and each had evidence of rupture of the aortic valve. Four of the patients died. This and other reports suggest that rupture of the aortic valve is more commonly seen in pneumococcal and staphylococcal endocarditis than in other forms of endocarditis.

A review of the hematologic changes in endocarditis was reported by Daland *et al.* (58). They stated that there is a wide variation in the leukocyte count, but that numerous histiocytes were often seen in the circulating blood with phagocytized red blood cells. These were seen more frequently in blood taken from the ear lobe than from the finger tip. There may also be toxic granulations of the neutrophils, especially in the terminal stages of the disease. A case illustrating the central nervous system manifestions of subacute endocarditis was reported by Antel *et al.* (59). The patient

presented with a toxic organic psychosis in association with a bacterial endocarditis due to *Streptococcus mitis* superimposed on syphilitic aortic valvular disease. Belli & Waisbren (60) reported that in 77 of 82 patients with subacute bacterial endocarditis, the first positive blood culture was obtained within the first five cultures. Fifty-two were diagnosed from the first culture that was drawn. In no case were more than ten cultures necessary. This paper de-emphasizes the need for taking blood cultures over a period of several days in the diagnosis of endocarditis, unnecessarily delaying treatment.

Miscellaneous Infections

Nineteen children with severe and fulminating infection following splenectomy, six ending fatally, are reported by Smith, *et al.* (61). All except two of the splenectomies had been performed for traumatic rupture. In no instance was there a decrease in the gamma globulin level. Seven of the cases had meningitis, five had acute benign pericarditis, five sepsis, one acute endocarditis, and one was undiagnosed. Another interesting observation was made by Waddell & Kunz (62) on nine cases of enteric infection in which salmonellosis occurred following previous gastric surgery. These cases represented 26 per cent of the salmonella infections in adults diagnosed in the Massachusetts General Hospital in 1954–55. In some cases the chronic enteric infection was the cause of symptoms which were ascribed to physiologic disturbances following surgery. This error was made commonly on those patients in whom vagotomy had been performed. It was felt that achlorhydria, relative or absolute, rapid transit, and changes in the normal flora or pH of the intestinal contents, might be factors which increased susceptibility. Two cases had wound infections with salmonella, one of which is not included in the nine cases of enteric infection.

An infection of the pleural space due to *Pasteurella multocida* was reported by Atin & Beetham (63). These organisms have been previously found in chronic lung infection and they are usually thought to be secondary invaders. In one patient the organism was isolated from empyema fluid; the infection responded to systemic and intrapleural penicillin therapy and repeated pleural aspirations. This species of *Pasteurella,* in contrast to most others, is usually sensitive to penicillin.

Additional cases of canicola fever in man contracted from infected pigs were reported by Coghlan, Norval & Seiler (64). These five cases among piggery workers were diagnosed during a five-year period. Forty per cent of the piggery workers demonstrated serologic evidence of previous infection with *L. canicola.* Of 75 pigs examined on one farm, 61 per cent had antibodies and of 78 on another, 40 per cent had antibodies to *L. canicola.* Spivack *et al.* (65) report on 11 cases of *Klebsiella* meningitis in the Philadelphia General Hospital. Of these 11, three cases were thought to arise from the middle ear, two in the lung, one from the frontal sinuses, one from the lower urinary tract. In seven of the cases the organisms were

typed and were either Types 1 or 2. All but one of the eleven cases died. A review of all of the previously reported cases is included in the article. LaBoccetta *et al.* (66) record a study of 609 patients with scarlet fever treated alternately with penicillin or sulfisoxazole with a control group of equal number receiving only aspirin and gargle therapy. Penicillin, given intramuscularly, was markedly effective in eradicating the streptococci from the nose and the throat; sulfisoxazole was not. Those patients treated with penicillin showed a smaller rise in antibody titer of antihyaluronidase and antistreptolysin than did the control group which was not treated, whereas those treated with sulfisoxazole had changes in titer similar to the control group. In none of the 609 patients did rheumatic fever or glomerulonephritis develop in either the control group, penicillin treated group, or the sulfisoxazole treated group.

Dedrick (67) recorded eight cases of *Listeria* meningitis with four fatalities. This paper emphasizes the difficulty in the immediate identification of this organism, since morphologically it closely resembles diphtheroids and may be discarded as a contaminant. The variation in the antibiotic sensitivity of the organism was emphasized; however, most of the strains were sensitive to the tetracycline group. Veronesi (68), recording from Brazil, reports clinical observations on 712 cases of tetanus with a review of the literature and comparison of four different treatment schedules. The patients most recently treated had a mortality rate of only 18.2 per cent. This paper describes a general outline of treatment, advocating no more than 100,000 units of tetanus antitoxin, continuous intravenous mephenesin (Tolserol) therapy, and chlorpromazine to produce "hibernation."

A paper by Geller, Chandler & Jawetz (69) emphasizes the occurrence of bacterial organisms which adapt readily to growth in cold environments and may readily contaminate stored blood in blood banks. Among those organisms which are capable of this are various strains of *Pseudomonas, Achromobacter,* and some *Aerobacter, Escherichia,* and *para-colobactrum.* They suggest methods of preventing this occurrence.

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FUNGAL INFECTIONS AND CHEMOTHERAPY[1]

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Sustained professional interest in systemic mycoses has resulted in reports of many individual cases and a trend toward the collection and reporting of comparatively large groups of cases. A most active medical interest in the search for effective therapeutic agents has been stimulated by the high mortality rates reported for several of the systemic mycoses. This review will consider primarily the discovery and application of specific therapy for the systemic mycoses, as presented in the English medical literature.

Convenient limits for the period to be covered at this time are set by the publication of other comprehensive reviews, particularly, the publication of the second edition of "Manual of Clinical Mycology" by Conant *et al.* in 1954 (1); "Symposium on Fungus Infections," Smith *et al.* (2); and "Therapy for the Systemic Fungus Infections," Smith (3). The monograph "Cryptococcosis (Torulosis)" by Littman & Zimmerman (4) published in 1956 also affords a convenient starting point for collection of data on that portion of the subject.

It will be apparent that the field of antifungal chemotherapy is being thoroughly tilled. New chemotherapeutic agents are coming to the attention of physicians at an accelerating rate. Although some sound achievements have resulted, particularly in the therapy of North American blastomycosis with the aromatic diamidines, and the therapy of actinomycosis with several antibacterial antibiotics, the situation as a whole displays more promise than accomplishment. A review at this time is therefore of particular interest to students of the subject. Toxicity for humans has proven to be a constant feature of antifungal antibiotics, and this aspect will require full treatment.

Since fungi are the cause of losses to food purveyors, laundries, agriculturalists, and silviculturalists, as well as the causes of disease in animals, research has proceeded in all these fields, as well as in pharmacy and medicine, for the discovery of antifungal substances but fields other than medicine have not yet furnished any significant number of prospective therapeutic agents. Nearly all of the prospective therapeutic agents that have been proposed were developed as the result of the search for antibiotics and chemotherapeutic agents carried on by pharmaceutical companies. Such research promises to be a major source of antifungal agents for use in medicine and for use in the other fields as well.

A summary (5) of the antifungal antibiotics, including a consideration

[1] The survey of the literature pertaining to this review was concluded in June, 1957.

of the microorganisms from which they were derived and their chemical characteristics, was brought up-to-date by Waksman in 1955 (6). Only a small proportion of those agents listed by Waksman were the subject of further publications, and few were applied to the therapy of human disease. Of the antibiotics mentioned by Waksman, only those used for therapy in man, or studied experimentally, or first described following 1955, will be considered below.

The review by Waksman shows that antifungal agents may be derived from bacteria, actinomycetes, or from other fungi, but that by far the largest number have been derived from actinomycetes. Their chemical natures vary, although most of those derived from bacteria are polypeptides, and one substantial group of those derived from actinomycetes are classifiable as polyenes. A majority of these antifungal agents are active against fungi only, but some are active against both bacteria and fungi. The chemical structures were described for only two agents, cycloheximide and Thiolutin, and only the first of these, cycloheximide, achieved clinical trial and will therefore be further described below. Waksman states that the possibility of finding antifungal antibiotics is highly promising. Another comprehensive list of prospective antifungal agents was assembled by Littman in the Monograph on Cryptococcosis mentioned above (4). Both of the above studies show that there is a tendency for antifungal antibiotics to have a broad application among the various species of pathogenic fungi, and it is reasonable to expect that any practical therapeutic agent in this field may have general application to more than one, or perhaps nearly all of the systemic mycoses.

Therapeutic Agents Used in Man

A list of 10 prospective antifungal therapeutic agents that have been reported upon in the recent literature, following use in the therapy of human disease, is given in Table I. The published concentrations producing inhibition of the growths of various pathogenic fungi are listed, as are the LD_{50} toxic doses for mice. Antifungal action has rarely been determined in a standard manner for different fungi. Such figures obtained by different observers and for different fungi by the same observers are often not strictly comparable. The fungi show through gross differences that some are highly potent as antifungal agents *in vitro* but most are unduly toxic to mice. Another list of 12 proposed antifungal agents that have not been used in man is given in Table II with similar data. For some of these the experimental data show that the substances are unsuitable for use in man.

Sulfonamides.—The sulfonamides, the first antifungal agents to be considered here because of their earlier chronological development, may be a surprise because they have seldom been considered previously in this connection. Mayer and his co-workers (7) have offered data to show that several sulfonamides, of which sulfadiazine is the best known, are active antifungal agents *in vitro,* using *Histoplasma capsulatum* as the test organ-

TABLE I

ANTIFUNGAL THERAPEUTIC AGENTS THAT HAVE ACHIEVED CLINICAL TRIAL FOR SYSTEMIC MYCOSES

THERAPEUTIC	Reference No.	INHIBITION IN VITRO μg./ml.						TOXICITY LD_{50} Dose in Mice in mg./kg. & Route in Administration
		B. dermatitidis	*C. immitis*	*C. neoformans*	*H. capsulatum*	*C. albicans*	*Sp. schenckii*	
Sulfonamides (sulfadiazine)	(7, 8)	1000			1000			1600 Orally & i.v.
Ethyl Vanillate	(13, 14)				200 to 400			1600 Oral (Rabbit)
Cycloheximide	(17)	>400		3.1	>400	>400		138 i.v.
Stilbamidine	(20, 22)	2.5		50	50			
2-OH-Stilbamidine		2.5		25	50			
2-Aminostilbamidine	(21)	5.0	25	250	125	250	250	
Beta-diethyl-amino-ethyl fencholate	(31)			500	100			72 i.v.
Brilliant green	(36)					0.02		
Nystatin	(17)	1.6	6.3	1.6	1.6	6.3		20 to 26 i.p.
Win 4227 (D 25) 5,5'-dichloro-2,2'-dihydroxydiphenyl sulfide	(57)					25		

ism. Fungistatic activity was noted in a concentration of 10 mg. per cent, and fungicidal activity in a concentration of 100 mg. per cent *in vitro,* while a daily dose of 2.5 to 5.0 mg. per mouse achieved survival rates of 100 per cent for 30 days. Acute toxicity in the mouse is slight, as indicated by the LD_{50} dose orally of 1600 μg. per ml. (8). These qualities are within the amounts that can be safely administered to man. Lamb (9) used triple sulfonamide mixtures and methyltestosterone to obtain arrest of two cases of blastomycosis and cure of another. These recent data, when added to the reports of single cases of cryptococcosis, or histoplasmosis, that recovered following sulfonamide therapy in the past, should lead to clinical studies adequate to show the optimal effects.

The role of sulfonamides in the therapy of nocardiosis is widely accepted (10), and further clinical case reports (11, 12) support the view that high doses persistently administered until all traces of nocardial lesions have disappeared are effective. Nocardiosis, however, is caused by a higher

bacterium rather than by a true fungus and this therapeutic application of the sulfonamides cannot be considered a true antifungal effect.

Ethyl vanillate.—Therapy of histoplasmosis with ethyl vanillate has been reported upon by several authors, beginning with Christie *et al.* (13), but without consistent evidence of therapeutic effects. The toxicity in animals was not excessive (14) but in man blood levels of 50 mg. per cent or over were associated with severe toxic symptoms and daily observation of blood levels was recommended. Single recoveries associated with therapy of cases with well-circumscribed late chronic lesions were observed, but where groups of cases of chronic pulmonary histoplasmosis were treated no favorable effects were found (15). It seems possible that ethyl vanillate administration was related to improvement in the systemic form of histoplasmosis, but opportunities for clinical trial in cases of systemic infection are few and prognosis in such cases is difficult. Under such circumstances only striking and invariably favorable results are readily interpreted in man and it is difficult to see how the use of a drug, found by some patients to be very difficult to take and with a narrow margin of safety, can be used in such a manner as to reach a definite conclusion as to its value in one of the less common clinical forms of the disease.

During a three-year period when 52 cases of coccidioidomycosis were seen by Fiese *et al.* (16), the treatment of seven of those with disseminated disease with ethyl vanillate resulted in cure of three, improvement in one, a stable course in one, relapse in one, and death in one case first treated when moribund; no definite conclusion was drawn from these observations.

Cycloheximide.—One of the first antifungal antibiotics to be studied *in vitro* and *in vivo* and to show properties suggesting the possibility of therapeutic effect in man was cycloheximide [or Actidione, $C_{15}H_{23}NO_4$; Brown & Hazen (17)]. This antibiotic is highly fungistatic *in vitro* for *Cryptococcus neoformans,* the inhibitory concentration being 3.1 μg. per ml. of medium. It is much less actively fungistatic for other pathogenic fungi. The fungistatic activity is inhibited by fresh serum and has not been demonstrable in animals. The intravenous toxic dose in mice is 138 mg. per kg. In man, dosage is accompanied by toxic symptoms such as emesis shortly after administration, but serious toxic effects have rarely been observed. Favorable therapeutic effects have not been regularly observed, although Carton (18) believes cycloheximide had some therapeutic effect and was the best therapeutic agent reported up to the time of his publication. The most recent report by Boshes *et al.* (19) was entirely negative. Cycloheximide has achieved a useful place as a laboratory reagent to aid in the diagnosis of fungal disease because it suppresses unwanted fungal growth in cultures.

Aromatic diamidines.—Stilbamidine, 2-hydroxystilbamidine, and 2-aminostilbamidine have been used more thoroughly than any other agents to be discussed in this review. Stilbamidine and hydroxystilbamidine were found to inhibit the growth of *Blastomyces dermatitidis* in concentrations

of 2.5 μg. per ml. (20), and aminostilbamidine was fungistatic in a concentration of 5.0 μg. per ml. (21). Higher concentrations were necessary for the inhibition of *H. capsulatum, Coccidioides immitis, C. neoformans,* and *Sporotrichum schenckii* (22). Favorable effects in the treatment of human North American blastomycosis were first observed with stilbamidine, but the use of this drug also resulted in a high incidence of peripheral neuritis affecting sensory innervation of the face. This toxic effect, as well as circulatory collapse associated with too rapid administration, was increased by exposure of stilbamidine or the patient to light rays, particularly ultraviolet light. Hydroxystilbamidine was less susceptible to the development of toxic products under the influence of light rays, and was found nearly devoid of neurotoxicity, but at the same time was approximately equally effective in its inhibitory effect for *B. dermatitidis* and other pathogenic fungi. A majority of observers found these antifungal agents effective in the treatment of North American blastomycosis. They do not achieve uniformly favorable results (23), and many of the publications since the latest edition of "Manual of Clinical Mycology" have been concerned with treatment failures in North American blastomycosis (24, 25, 26), and with inconclusive therapeutic trials of diamidines in coccidioidomycosis (27), in histoplasmosis (28, 29), and in sporotrichosis (30). One of the cases of sporotrichosis died with diffuse, subacute glomerulonephritis, possibly because of the hydroxystilbamidine. This is the only report of a serious toxic complication, and symptoms of renal toxicity have only rarely been observed. The author postulated an allergic state of sensitivity in the patient. The absence of adequate therapeutic effects in certain cases deserves more study. Harrell *et al.* (26) postulated that the immune state of the patient was the determining factor in the therapeutic effects of the drugs. Hydroxystilbamidine remains the therapy of choice in North American blastomycosis but requires further studies of its actions and limitations in order that prognosis may be better understood.

A third member of the aromatic diamidine group, 2-aminostilbamidine, is also administered parenterally. It was used in the treatment of five cases of coccidioidomycosis by Kushner *et al.* (21) in doses of from 2.3 to 10 gm. each. The drug produced some yellow discoloration of the skin and nausea and vomiting. Some suppression of the manifestations of chronic pulmonary coccidioidomycosis was noted in two cases, but in coccidioidal meningitis no curative effect was found. The authors refer to studies showing that none of the fluorescence, characteristic of stilbamidine, was detectable in the spinal fluid when that drug was used, and state that lack of effect of aminostilbamidine in meningitis may result from inability of the drug to pass the blood-brain barrier. They discuss the characteristic fluorescence of 2-aminostilbamidine which is somewhat greater than that of the other aromatic diamidines, and which is the basis for detection of the presence of the drug in tissues and excretory fluids. Direct evidence that 2-aminostilbamidine was deposited within the cells of the liver, the adrenals, and the

kidneys, was obtained by photomicrographs showing fluorescence of nuclear inclusions and cytoplasmic granules during illumination with ultraviolet light. They also showed illustrations of histologic sections demonstrating the deposition of 2-hydroxystilbamidine within the spherules and endospores of *C. immitis,* indicating the incorporation of the compound in the microorganism. The chemical relationships of these compounds with ribose nucleic acids and their affinity for nuclear structures in the animal body lend strong support to the hypothesis that they inhibit the growth of microorganisms through competitive metabolic reactions within the cell and in nuclear structures.

Beta-diethyl-aminoethyl-fencholate.—An antihistaminic, β-diethyl-aminoethyl fencholate, designated MRD-112, was described in two reports of individual cases and in two reports dealing with groups of cases. This experimental drug has a complicating mild sedative effect. Antifungal action was demonstrated by Ludwig *et al.* (31) *in vitro* in a concentration of 100 μg. per ml. The LD_{50} intravenous toxic dose for mice was approximately 72 mg. per kg. Michael & Vogel (32) noted an equivocal therapeutic effect in a case of systemic histoplasmosis and MacKinnon & Callander (33) noted what appeared to be a complete cure of a case of disseminated histoplasmosis, although the patient subsequently relapsed a year later with tuberculous infection of the knee. Polk *et al.* (34), and subsequently Lehan *et al.* (35), reported inconclusive results in two series of histoplasmosis cases, numbering 5 and 12, respectively, without appreciable favorable therapeutic effects. The first-named authors (34) noted that four of five cases showed varying degrees of liver degeneration at biopsy, and one additional case who died of pseudomembranous enteritis was also found to have toxic hepatitis and toxic nephrosis. Six cases treated with β-diethyl-aminoethyl fencholate were reported by Sutliff (15). These cases received from 150 to 600 mg. per day for periods of one or two months. No favorable effect was noted in five. In one case of chronic pulmonary histoplasmosis of minimal severity seen relatively early, improvement followed fencholate therapy, and in one case of disseminated histoplasmosis marked improvement followed fencholate therapy. It may be significant that with β-diethyl-aminoethyl fencholate, as with ethyl vanillate therapy, improvement was noted in one case each with disseminated lesions. It is questionable whether sufficient further opportunity to follow up this line of investigation will be found, in view of the constant availability of promising antifungal therapeutic agents. The data would appear to be adequate to show that no satisfactory therapeutic effects can be anticipated in the treatment of chronic pulmonary histoplasmosis with β-diethyl-aminoethyl fencholate.

Brilliant green.—A single case report dealing with an otherwise little studied therapeutic agent, namely brilliant green dye administered by aerosol, is worthy of note. Smith & Armen (36) reported a case of pulmonary moniliasis due to *Candida albicans* which was cured by brilliant green aerosol therapy, in which the etiologic relationship of *C. albicans* had

been thoroughly demonstrated by cultures of pulmonary biopsies of pleural fluid. Only one previous case of record treated with brilliant green was known to the author. This observation deserves further development. Critical consideration of diagnoses of candidiasis, the administration of brilliant green dye and, also, the consideration of the possible use of aerosol route for other antifungal agents are worthy of further application.

Erythromycin.—The treatment of actinomycosis caused by *Actinomyces bovis* was reviewed by Harvey *et al.* (37), in connection with a report of the experience at the Johns Hopkins Hospital in which the recommendation was made that large doses of penicillin and indicated surgery were the therapeutic modalities of choice. There was also a series of reports with satisfactory therapeutic results in moderate numbers of relatively mild cases following the employment of streptomycin, chlortetracycline, oxytetracycline, stilbamidine, and isoniazid. All of the above modes of therapy were critically examined by Herrell *et al.* (38), and the possibility was suggested as the result of experimental studies and as the result of the treatment of four cases, that erythromycin might have some advantages. *A. bovis* was found to be extremely sensitive to erythromycin by Suter & Vaughan (39), and by Herrell (38). The results were quite satisfactory in three cases of cervicofacial actinomycosis receiving 300 mg. of erythromycin every 6 hr. for 3 to 4 weeks, with the addition of surgical removal of an infected mass in one, and the addition of high dosage penicillin for a second who had complicating actinomycotic osteomyelitis. In a fourth case with a rectal abscess, similar dosage for 7 weeks and evacuation of the abscess achieved a satisfactory result. It is apparent that, whereas the over-all effects of penicillin and penicillin with adjunctive surgical therapy in actinomycosis can be comprehensively described on the basis of adequate data, none of the other promising therapeutic agents have had as complete a study. It seems possible that erythromycin may prove superior to the others if a clinical trial can be accomplished.

Nystatin.—An antibiotic, nystatin (Mycostatin, Fungicidin), was described by Hazen & Brown (40). This antibiotic was elaborated by *Streptomyces noursei,* a strain which may also produce cycloheximide, described above (17). The antifungal spectrum of nystatin shows inhibition for many pathogenic fungi in from 1.6 to 6.3 μg. per ml. It is toxic for mice in an LD_{50} dose of 20 to 26 mg. per kg. intraperitoneally. This antibiotic has been used widely and has been found to be effective for infections that do not require parenteral administration, or oral absorption, such as candidiasis of the accessible body cavities and skin. The drug is poorly absorbed following oral administration. Experimental studies in the therapy of animal infections were reported by Campbell *et al.* (41, 42) for coccidioidomycosis, histoplasmosis, cryptococcosis, and sporotrichosis in mice, in which the survival time was prolonged by subcutaneous 1 mg. daily doses of nystatin, and by Steinberg *et al.* (43) and Hazen *et al.* (44) for candidiasis in mice. Baum *et al.* (45) compared amphotericin B and nystatin alone and with

sulfonamides in hamsters infected with *H. capsulatum*. Prolongation of survival was attained and was improved by the addition of sulfonamide to the antibiotic therapy. The partial elimination of monilia from the stools in man was reported by Hewitt *et al.* (46), Gimble *et al.* (47), and Spaulding. *et al.* (48) by the administration of nystatin orally as an adjunct to tetracycline or neomycin-polymixin therapy. In the study reported by Stone & Mersheimer (49), neither the patient nor the doctor was informed as to the contents of capsules administered to the patients, and side effects were less in the tetracycline-treated patients who also received nystatin 3.6 per cent, as compared with 11.1 per cent in those who received only tetracycline. In six of these cases, vaginal moniliasis appeared as a complication in patients treated with tetracycline alone, and no such cases were observed in the patients treated with tetracycline combined with nystatin. The reports presented in a symposium "Therapy of Fungus Diseases" edited by Sternberg and Newcomer were quite uniform in their data on favorable effects of nystatin in candidiasis. Dobias (50) reported that nystatin was a very useful substance in the treatment of cutaneous moniliasis in 70 children. Drouhet (51) reported favorably on the treatment of 43 cases of candidiasis. Graham *et al.* (52) treated patients topically with nystatin using troches, tablets, powders, solutions, gels, suppositories, and ointment interchangeably for 94 patients with *C. albican* infections, 30 with oral lesions, 15 with vaginal, and 49 with various cutaneous lesions. Graham *et al.* (52) also treated 93 patients with various dermatophytoses; 60 with *Trichophyton rubrum,* 26 with *Trichophyton gypseum,* 3 with *Microsporum lanosum,* and 1 each with *Microsporum fulvum, Microsporum furfur, Epidermophyton floccosum,* and *Trichophyton tonsurans.* Clinical response was often dramatic in cases of thrush and perleche. The lesions frequently disappeared within 48 to 72 hr., but, in general, clearing occurred within two to three weeks in other localized infections. The results of treatment of dermatophytoses were generally less dramatic, the average period of treatment being three months. Several other authors reported favorable results in the treatment of candidiasis (53, 54, 55). The authors concluded that nystatin gave good to excellent results when used for the treatment of moniliasis, but was less effective when used for superficial dermatophytoses.

Nystatin has been used in systemic mycoses; coccidioidomycosis and histoplasmosis, but without striking therapeutic effects. Newcomer *et al.* (56) reported the treatment of five cases using intravenous preparations. Three of these improved sufficiently to be declared inactive, but in two cases of meningitis no therapeutic effect was observed. The intravenous preparations were used because orally administered drug was not well absorbed, and because intramuscular preparations frequently produced chills, severe pain and tenderness at the sites of injection and, in a few cases, abscesses and draining sinuses. The use of intravenous preparations was associated with frequent chills and fever. Lehan *et al.* (35) reported

briefly on the use of nystatin in four cases of histoplasmosis and one of coccidioidomycosis but without adequate favorable therapeutic effects.

In summary, nystatin was particularly effective in moniliasis which was accessible to topical therapy. In spite of the broad spectrum of antifungal activity of nystatin its therapeutic effects in systemic mycoses have been disappointing, possibly because of the fact that its toxicity prevents the exhibition of adequate quantities of the drug.

5,5'dichloro-2,2'dihydroxydiphenyl sulfide.—An experimental drug, 5,5'dichloro-2,2'dihydroxydiphenyl sulfide, was used orally in Germany for several cases of skin mycoses and was reported by Seeliger & Reifferscheid (57) as effective in the treatment of maduromycosis caused by *Monosporium apiospermum.* This therapeutic agent is difficult to characterize because of differences in the terminology related to etiologic agents and clinical entities in the original articles. Further study of the antifungal spectrum and toxicity in mice may show that this drug compares favorably with others under active investigation.

Therapeutic Agents Studied *in vitro* and *in vivo* in Animals

The intense activity which led to the trial of 10 different antifungal agents in the therapy of systemic mycoses during the brief period covered by this review was sustained by the continuous discovery of antifungal agents in even greater numbers. During the same period, 12 such potential antifungal therapeutic agents for systemic mycoses were reported and are listed in Table II. Several of these compounds were less completely studied than others, several had characteristics which raised questions about their antifungal effects, and several were shown to be unsuitable or at least much less suitable than others for therapy in man because of toxicity. On the other hand, some possess characteristics which suggest the possibility of successful application to human disease.

Substances whose suitability for clinical trial is not clear.—Tetraethylthiuram disulfide (Antabuse) was chosen as the best substance related to rhodanine by Christison *et al.* (58), who found that a number of such compounds were highly active antifungal agents *in vitro.* Further use of this drug was discouraged by the finding that intraperitoneal administration did not protect mice against experimental histoplasmosis. Chlorquinaldol (5,7-dichloro-8-hydroxy-quinaldine) was studied by Littman (59) and shown to be more potent than either vioform or nystatin in inhibiting the growth of *C. albicans.* The pharmacology of the drug was not completely described. Experimental use by Shidlovsky *et al.* (60) showed an additive effect to neomycin for inhibiting the intestinal microbial flora of man. A relatively unstable antifungal antibiotic derived from *Streptomyces ruber,* called mycoticin, was reported by Burke *et al.* (61). This antibiotic needed to be stored *in vacuo* to maintain its potency. The antibiotic filipin with the characteristics of a polyene derived from *Streptomyces filipinensis* by Gottlieb (62) was briefly reported. Curtis (63), following a study of a num-

TABLE II

PROPOSED ANTIFUNGAL THERAPEUTIC AGENTS THAT HAVE NOT ACHIEVED CLINICAL TRIAL FOR SYSTEMIC MYCOSES

THERAPEUTIC DOSE	Reference No.	INHIBITION IN VITRO μg./ml.						TOXICITY LD_{50} Dose in Mice in mg./kg. & Route of Administration
		B. dermatitidis	*C. immitis*	*C. neoformans*	*H. capsulatum*	*C. albicans*	*Sp. schenckii*	
Tetraethylthiuram disulfide (Antabuse)	(58)	200			5.0	100		
Chloroquinaldol	(59)	3.0	6.0	3 to 10	1 to 3	1.5	6.0	500 Oral
Mycoticin	(61)	2 to 4	2 to 3	6 to 8	1 to 2	6 to 10	1 to 3	10 to 26 i.p.
Filipin	(62)	31.0	15.0	1.0	8.0	8.0	8.0	
p-methoxy-beta-methyl-beta-nitrostyrene	(63)	1.0						130 i.p.
Mycolutein	(64)			6.3		2.8		25 to 50 i.v.
Eulicin	(65)	0.04		0.07	0.07			3 i.v.
Fungichromin	(66)	0.8				6.3		16.4 i.p
PA-132	(67)				100			
Ascosin	(68)			1.2	1.6			6.3 i.v.
Antibiotic 1968	(70)			1.9		3.9	3.9	250 i.v.
Amphotericin B (Fungizone)	(72, 73)	0.5	0.5	0.63 0.06	0.04 0.5	0.5 3.7	0.14	30 i.v.

ber of aromatic diamidines, cinnamic acids, and nitrostyrenes, described the characteristics of *p*-methoxy-methyl-beta-nitrostyrene, as in Table II. The addition of whole blood decreased the antifungal activity of this agent and it was ineffective in animal protection experiments. Preliminary trial in one patient was not encouraging. Only a few details are known about mycolutein, which was described by Schmitz & Woodside (64) as in Table II. Further studies are necessary to determine its potential value.

Substances with greater than average toxicity in vivo in animals.—An antifungal antibiotic, eulicin, was isolated from a species of streptomyces by Charney *et al.* (65) and was found to have antibacterial and antifungal properties. Its toxicity for mice was such, as indicated by an LD_{50} dose of only 3 mg. per kg. intravenously, that only the more highly sensitive fungi

listed in Table II, or certain bacteria, were believed to be useful for therapeutic application. Fungichromin from *Streptomyces cellulosae* is a polyenic compound, reported by Tytell *et al.* (66), with characteristics as listed in Table II. Further study is necessary to determine its potential value. An antibiotic, called PA-132, was reported by Koe *et al.* (67) but its toxicity for mice in therapeutic doses was believed to preclude its use in man, although an eventual therapeutic trial in plant diseases was foreseen. An antibiotic derived from *Streptomyces canescus,* named ascosin, was found to be too toxic for parenteral use in man, following studies by Hickey *et al.* (68) and Emmons & Haberman (69) as indicated in Table II.

Antibiotic 1968.—An antibiotic called 1968 derived from *Streptomyces aminophilus* was reported by Oswald *et al.* (70) to have the activities recorded in Table II and to be relatively nontoxic in mice, and by Campbell (71) to prolong survival in mice infected experimentally with *H. capsulatum, Sp. schenckii* and *C. albicans.* This agent appears thus far to be a potentially useful therapeutic agent in man.

Amphotericin B.—An antibiotic complex, amphotericin A and B, was described by Gold *et al.* (72) and has reached the threshold of wide clinical trial. No clinical report of its use in systemic mycoses has yet been published. This antibiotic was derived from a streptomycete culture, #$M_4$575, which was collected in the Orinoco region of Venezuela. It was not antibacterial but had a wide spectrum of antifungal activity in preliminary testing, as shown in Table II. The antifungal potency of amphotericin B was found to be greater than that of amphotericin A, and subsequent studies were concerned only with amphotericin B. Amphotericin B was relatively insoluble in water but was readily dissolved in dimethylsulfoxide to 30 to 40 per cent. A crystalline product was obtained. The chemical structure was that of a polyene. The proprietary name fungizone was selected for the product. Its toxicity in mice was indicated by the LD_{50} dose of 30 mg. per kg. (73). *In vitro H. capsulatum, B. dermatitidis, Blastomyces brasiliensis,* and *C. neoformans,* as well as the dermatophytes, *Microsporum audouini, E. floccosum,* were susceptible and protection was afforded in mice against infection with *C. immitis* and *C. albicans.* Sternberg *et al.* (74) showed protection for mice infected with *H. capsulatum* and *C. neoformans.* Louria *et al.* (75) concluded that amphotericin B showed considerable promise of adding significantly to the armamentarium of antifungal agents effective in human disseminated mycoses following an experimental study of its effects on *H. capsulatum* and *C. neoformans in vitro* and *in vivo* in animals. Preliminary clinical studies of its oral administration in coccidioidomycosis and cryptococcosis by Halde *et al.* (76), and of its effect on the number of *C. albicans* colonies in the stools of patients treated with tetracycline by Halde *et al.* (77), and a comparison of the activity of nystatin and amphotericin in the treatment of superficial infections with *C. albicans* in children were reported [Kozinn *et al.* (78)].

The wide antifungal spectrum of *in vitro* inhibition by amphotericin B,

and its activity in the systemic animal and superficial human infections which are reported are sufficient to give this antibiotic the most favored place among currently available experimental antifungal antibiotics. Its toxicity in mice is such as to serve as a warning to investigators to look for reactions as the dose is increased.

The avid development of antibiotics and chemotherapeutic agents for pathogenic fungi has had a weighty impact on the current management of systemic fungal infections. Concomitantly, with the wide acceptance of antibiotic therapy of actinomycosis, the sulfonamide therapy of nocardiosis, and aromatic diamidine therapy of North American blastomycosis, an ever greater proportion of cases of systemic mycoses are being diagnosed specifically with the aid of culture methods relatively early in their clinical course. New potential therapeutic agents are being developed annually which have antifungal potency *in vitro* and *in vivo* in animals in concentrations that can be readily attained in man, and toxic effects in animals as mild as those of widely used antibiotics. Careful selection of potential antifungal therapeutic agents for clinical trial, and their systematic administration, are widely practiced and should lead to the maximum amount of progress in this field.

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INFECTIOUS DISEASES (VIRUSES)[1]

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The technical development of virus research during the last half dozen years has produced a virtual revolution in our attitude to human viral disease. The implications of this revolution are still to be clarified, both at the biological level and at the clinical-epidemiological level. At the present time, it seems at least as important to outline broadly the situation which has developed as a result of the success of the tissue culture methods for virus isolation and study, as to provide an account of the types, distribution, and significance of the viruses now being isolated from human materials.

From the biological angle, the present position is perhaps what ought to have been expected. It is the rule in Nature to find that most ecological niches are filled by a variety of organisms which contrive to survive together in the particular environment. Where parasites and micro-symbionts are concerned, the standard situation, subject however to conspicuous exceptions, is a harmless coexistence with the host. This means that the existence of parasite or symbiont will only be recognised when adequate methods are available for its demonstration in or on the apparently normal host. It was to be expected, therefore, that when methods became available by which viruses could be recognised and isolated by methods not involving the production of manifest disease in human or other mammalian hosts, many "silent," almost symbiotic, viruses should be obtained.

The refinement of tissue culture methods by which effects due to virus growth (delayed effects as well as acute cytopathogenic action) can be recognised with relative ease has allowed this to be realised in regard to at least three humanly important ecological niches. These are (*a*) the alimentary tract; (*b*) the respiratory tract; and (*c*) the complex situation exploited by the athropod-borne viruses. In each instance the relevant environment should, strictly speaking, be expressed in terms which should also include the distribution and density of available hosts, the obstacles to transfer of virus from one host individual to another, and the influence of immunity on susceptibility to infection. All these are included in the concept of an ecological niche in which a virus species or type may survive.

In each type of ecological situation we have now uncovered a wide variety of viral types, very few of which produce overt disease as a result of their "standard," usually rather short lasting period of multiplication in host cells. Most of the important viruses in these three ecological regions produce disease as a result of invading some organ distant from the site of primary multiplication. In each group there are viruses which have never

[1] The survey of the literature pertaining to this review was concluded in July, 1957.

been proved to cause human illness and others in which any symptoms produced are trivial.

From the clinical and epidemiological angle, this flood of new discovery has proved almost an embarrassment. We have reached the stage where a well-equipped research laboratory can produce an etiological diagnosis for most viral infections, severe or trivial. The large number of serological tests and other manipulations needed to identify an isolated virus, however, makes the procedure time-consuming and expensive. Particularly in communities with limited resources it is becoming necessary to weigh the pros and cons of the new situation. We can try to balance the advantage to the public health administrator and the gratification to the teacher of medicine of knowing what viruses are active in the community, against the fact that the physician's treatment of the patient with viral disease is uninfluenced, except in the rarest instances, by the laboratory diagnosis. The interest and value of research on the minor virus diseases is incontestable; its application to the practical problems of preventive and curative medicine is not always so apparent.

It is from this slightly sceptical angle that an attempt is made to cover the more important developments in the last 2 to 3 years. To avoid overlap, topics dealt with in the reviews by Scott (77), Jackson (43), and Jordan & Dingle (47) are avoided or touched on very lightly unless highly significant work has appeared in the interim.

Respiratory Viruses

In view of Jackson's review covering the literature of this field to July, 1955, only significant subsequent findings will be considered.

The adenovirus group.—The name adenovirus proposed by Enders *et al.* (24) has now been generally accepted for the viruses previously referred to as APC, RI-67, or ARD viruses. The group is defined by the ability to grow in suitable tissue cultures, usually monkey kidney or HeLa cells, with characteristic degenerative changes in the cells, and by the possession of a complement-fixing antigen common to the whole group. Neutralization tests using tissue culture methods and (rabbit) immune sera indicate the existence of at least 14 serotypes, 12 of which have been obtained from human tissues and two from monkeys (70).

The epidemiological characteristics of the types have now been considerably clarified and with the qualification that many nonsymptomatic infections undoubtedly occur, the position during the period 1954-56 has been approximately as follows:

Viruses of Types 1, 2, 5 and 6 are those characteristically found in cultures made from adenoid tissue removed surgically from children. They may be isolated from minor febrile, respiratory, and pharyngeal infections, particularly in children (46) but have not been observed in military outbreaks of respiratory infection. Infection of volunteers with Type 1 adenovirus has been achieved by Roden *et al.* (67) in England.

Types 4 and 7 adenovirus are responsible for a large proportion of acute respiratory disease among recruits entering American Army establishments in the winter months. In the early months of 1956, Hilleman *et al.* (37) found that 90 per cent of the respiratory disease at Fort Dix, New Jersey, was due to adenovirus infection, and of 41 strains isolated 59 per cent were Type 7, and 41 per cent Type 4. Clinical disease varied but included a proportion with the primary atypical pneumonia syndrome (38). Type 3 may also be involved and in another survey Hilleman (36) found 20 per cent of the adenovirus infections owing to this type.

By contrast, infections resulting from these viruses were not common in a middle class civilian study group in Cleveland (46), only 10 adenoviruses being isolated from 531 pharyngeal swabs taken from respiratory infections in this group during 1954-55. Evans & Morse (25) found that 8.5 per cent of students admitted to hospital for febrile respiratory infections showed evidence that adenoviruses were responsible. Price (63) in Baltimore found about 4 per cent of persons showing serological evidence of adenovirus infection during a year.

The military importance of adenovirus infection among recruits in the winter, plus the evidence for postinfection immunity, has stimulated work on artificial immunization against adenovirus Types 4 and 7. Hilleman *et al.* (37) prepared a bivalent formalin-killed vaccine from infected monkey kidney tissue cultures. Tests against a control series receiving a placebo injection showed a highly significant protection which became evident during the second week after the initial inoculation. In a more detailed account of the same investigation, Stallones *et al.* (81) found that serological diagnosis of all hospitalized cases revealed that in the vaccinated group there was only one case of adenovirus infection requiring hospitalization, as against 61 such cases in the control series receiving placebo only.

Studies of the incidence of adenovirus infections among United States Navy recruits have been reported by Woolridge *et al.* (90) and by Rowe *et al.* (72) with results generally similar to those seen in the Army. At the Great Lakes Training Station in early 1954, approximately 10 per cent of the cases admitted with febrile respiratory infection yielded Type 4 adenovirus (72).

Type 3 is characteristically responsible for what Bell *et al.* (5) have called pharyngoconjunctival fever. This is not infrequently seen in civilian groups, occurring particularly in children during the summer time. The cases present with fever, constitutional symptoms, mild pharyngitis, cervical lymph node enlargement and conjunctivitis (22, 29). On occasion the eye symptoms can be severe. Cockburn *et al.* (13) provided retrospective serological evidence that an epidemic of conjunctivitis in Greeley, Colorado, in 1951 was due to adenovirus Type 3. In some of the patients corneal opacities developed as well as signs of general infection. Ginsberg *et al.* (29) found in their studies that the virus did not spread easily to those exposed to patients. Furthermore, the virus was isolated only from patients with

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symptoms, and serologically demonstrable subclinical infection was uncommon. Transmission of infection to volunteers is most readily accomplished by lightly swabbing the conjunctiva with infective tissue culture material (41, 87). There is a well-marked antibody response after infection and a high correlation of resistance to experimental infection and the presence of circulating antibody. In cases of nonbacterial pharyngitis occurring in Cleveland in the summer of 1954, Type 3 was the commonest agent isolated, being responsible for about 14 per cent of the cases (46). Conjunctivitis was not prominent. Sabin (73) records a personal communication from Svedmyr that a Type 3 adenovirus epidemic in Kumla, Sweden, showed a high proportion of cases with diarrhea.

The acute keratoconjunctivitis that was prevalent in industrial establishments on the west coast of the United States during the war period, 1939–45, has now been conclusively associated with adenovirus Type 8 by Jawetz *et al.* (44). The association is world-wide, specific antibodies having been observed in patients contracting the infection in Japan, Italy, Switzerland, and North America. In 17 of 18 patients from whom serial specimens were available, a rise in neutralizing antibody was observed. None showed rise in antibody against Type 3. Somerville (80) has reported extensive outbreaks of keratoconjunctivitis due to Type 8 infection in shipyard workers in Scotland during 1955 and 1956. This serological type has not been observed apart from the clinical disease. Types 9, 10, and 11 are based on strains from cases of human disease but no specific correlation with any particular disease has been recorded.

Influenza viruses.—Until the recent appearance of what can be referred to as Asian A (1957) influenza, there has been little variation in the clinical and epidemiological behaviour of influenza from the pattern of earlier years. According to Isaacs, writing in 1956, there had been no major outbreaks of influenza since 1953 (42). Typical local epidemics, however, had occurred in many parts of the world. In Baltimore in 1954–55, an influenza B epidemic involved about 20 per cent of the students and nurses under observation (63). Influenza A produced cases in various parts of the Northern hemisphere in the winters of 1954–55 and 1955–56 (42) and an extensive but relatively mild epidemic occurred in Australia in May-June, 1956.

At the time of writing this review, relatively little has been published concerning the extensive outbreak of a new serotype influenza A in Asia which first created world wide interest when it appeared at Singapore in May, 1957. Subject to correction when more extensive information is available, this epidemic probably started in Northern China in February or March of 1957 and reached Singapore by way of Hong Kong. It then spread widely in Asia and in July had caused extensive epidemics of mild influenza in Australia. The virus is readily isolated by amniotic inoculation in chick embryos, possesses the soluble antigen of other A strains, but is serologically quite distinct from any of the extant A subtypes. In areas like Malaya the incidence has been very high but the great majority of cases were mild (34).

Most interest and discussion during the last two years has been centred

on the nature of the serological differences observed between strains of influenza A from different epidemics. Isaacs (42) considers that since 1950–51 two serologically distinct subtypes, Liverpool (L) and Scandinavia (S), have each evolved to produce new serological types, both of which were widespread in 1955–56. In his view the L strains have given rise to "Eire 55" present in 1954–55 in England, Eire, India, and New York State, and in 1955–56 in England, Naples, India, and South Africa. The S strains may have been ancestral to a sharply distinct variety "Dutch '56" isolated in February-March, 1956, in Leiden, Holland. Within a few months, similar strains were received by the World Health Organization Influenza Centre from India, Canada, East Africa, and South Africa.

Jensen (45), however, does not believe that any special importance should be attached to the S and L lines since, among the strains isolated since 1946, there have been many with just as marked individual serology. In his review of serological data on influenza A strains isolated since 1933, Jensen concludes that it is legitimate to divide strains into three major families. The prototypes selected are Swi 15 (the classical strain of Swine influenza virus) and the two commonly used American strains, PR8 and FM1, representing families of which the first strains isolated were WS and CAM, respectively. The relatively small number of porcine strains available are remarkably uniform serologically and very distinct from those of the other two families. Within the PR8 and FM1 families there are wide ranges of antigenic individuality and Jensen finds nothing to convince him that there has been any progressive change in serological character over the period when each family was dominant. This is at variance with most of the opinions expressed by earlier workers. The fact of serological change is established and current opinions can be grouped into three.

The appearance of Asian A (1957) virus may soon allow a clearer picture of the process of influenza virus evolution but it is too soon yet to offer any firm opinion as to which of the three current views is the most satisfactory. The first of these, originally due to Andrewes (2) and elaborated by Burnet (8) under the term "immunological drift," holds that the changing pattern is owing to the advantage of serological novelty for survival of a virus that must infect populations partially immune from past infection by similar viruses, and that there is no necessary limit to the emergence of new serological types. The second adopts the same general interpretation but would replace the idea of serological novelty with the emergence of one or other of the limited number of serological patterns that are within the capacity of its genotype to produce. This is supported by Francis (26) and has the important practical implication that when examples of all the possible strains have been obtained a vaccine effective against all possible types of influenza A could be prepared. On the first hypothesis this would be impossible. The third may be called the agnostic approach of Jensen (45) who defines the challenge to be met as the emergence of a new family at an unpredictable time.

The work of Davenport *et al.* (17) on the persistence of the immunologi-

cal pattern of the virus first encountered in human antibody has been extended. The results from England showed the same trend as in the United States (18), persons over 30 years showing dominance of Swine antibody, between 12 and 30 years to the classical A strains, and under 12 years to the A prime strains that appeared around 1946–47. Similar evidence of the persisting serological orientation of early influenza virus infection was found in groups containing persons of different ages who were inoculated with monovalent influenza virus A vaccine (16). There is now a general trend toward the concept suggested many years ago by Laidlaw (52) and supported by Shope (78) that the dominant component of the 1918-19 pandemic was closely related serologically to "Swine" strains.

If any "cyclic" view of the serological changes in influenza A is correct, the rather rapid disappearance by death of persons with "Swine" antibody in the next decade should allow the re-emergence of that type as a dominant cause of human influenza. This would, on the other hand, be extremely unlikely if there is a relatively unrestricted capacity of the virus to produce new immunological patterns.

Other respiratory viruses.—Workers in Toronto and Cincinnati have independently isolated a new type of myxovirus from cases of infantile croup which has strong claims to be regarded as the etiological agent of at least some of these illnesses in children. In Toronto, Morgan *et al.* (60) observed 70 cases of laryngo-tracheo-bronchitis admitted to the Hospital for Sick Children and from five of these isolated cytopathogenic viruses in tissue culture. With improved techniques in 1955, similar agents were isolated from 10 of 15 cases studied. These have been found serologically similar to those described by Chanock (12). He obtained from throat swabs taken from infants with croup a cytopathogenic agent producing a peculiar "sponge-like" degeneration in monkey kidney and human amniotic cell sheets. This was transmissible in series and specific neutralization of the cytopathogenic effect was obtained with serum from 5 of 12 children recovered from illness of this type. The virus agglutinated chicken red cells, attaching to receptors which were sensitive to destruction by the cholera vibrio enzyme RDE (receptor-destroying enzyme), and grew poorly but significantly in the amniotic cavity of the chick embryo. For these reasons it is regarded as belonging to the myxovirus group. No serological relationship could be demonstrated to influenza viruses A, B, or C, Newcastle disease, or Sendai virus but there may be a partial serological resemblance to mumps virus.

Price (62) has isolated a virus (JH) producing a slowly developing cytopathogenic effect on monkey kidney tissue cultures. It was isolated from patients in Baltimore with minor febrile upper respiratory tract infections and has been shown to provoke a specific antibody response in the persons from whom it was isolated. It has no pathogenicity for laboratory animals, including infant mice and hamsters and chick embryos, and shows no relationship to any of a wide range of cytopathogenic viruses. It is defi-

nitely not in the adenovirus group. The fact that 20 per cent of persons over eight years of age possess antibody suggests that widespread infection occurs.

Viruses Characteristically Present in the Intestinal Tract

Poliomyelitis.—In view of the great amount of readily accessible literature on poliomyelitis and its prevention by Salk-type vaccines, this topic will not be considered in this review. Attention may be drawn to an important review of the pathogenesis of poliomyelitis by Sabin (74) and to the papers by Dick and associates (21) dealing with the regular isolation from stools of persons given orally live attenuated virus, of strains much more virulent for monkeys than the strains administered. Estimates of the effectiveness of Salk vaccine and recommendations for its most effective use will be found in papers by Langmuir *et al.* (53) and Salk (75, 76).

The ECHOviruses.—It has been known for some years that "orphan" viruses producing cytopathogenic effects similar to polioviruses in tissue culture of monkey kidney, but serologically unrelated to any of the polio viruses, could occasionally be isolated from the bowel in a variety of clinical conditions as well as from normal persons. The viruses fall into a number of serologically distinct groups, have been named ECHO viruses (enteric-cytopathogenic-human-orphan), and defined as including viruses (*a*) cytopathogenic for monkey and human cells; (*b*) not neutralized by polio virus antisera; (*c*) not pathogenic for infant mice; and (*d*) unrelated serologically to other known groups of viruses. Thirteen immunological types are accepted (14) but more will undoubtedly be added.

Most workers have found that ECHOviruses are significantly more frequent in faeces from cases of "nonparalytic polio" than from polio cases or normal individuals, and there are enough instances in which correlated antibody rises have occurred to provide strong evidence for an etiological association.

One of the clearest examples of the part played by an ECHOvirus in producing aseptic meningitis is provided in Davis & Melnick's study (19) of cases diagnosed as paralytic and nonparalytic polio in vaccinated and unvaccinated subjects. In the nonparalytic polio group there was a striking difference between vaccinated and unvaccinated subjects. In the unvaccinated group there were 45 cases from which virus was isolated, 23 polio viruses, 9 ECHO Type 6, with 13 other viruses being obtained. From vaccinated individuals with the same syndrome, 24 virus strains included 5 polio, 15 ECHO, and 4 others. There was no clinical evidence of any difference between the nonparalytic infections caused by polio and ECHOviruses. Similar findings were reported from Sweden by Svedmyr (82) who found 36 per cent of the cases of aseptic meningitis studied resulted from ECHOviruses.

In a valuable general survey of the position, Sabin (73) points out that in low socio-economic groups, viruses of all the intestinal types, polio,

Coxsackie, and ECHO, are most frequently isolated in the young. In Cincinnati, for instance, the rates for ECHOviruses by age were 1-4 years, 5.2 per cent; 5–9 years, 2.6 per cent; 10–14 years; 0.2 per cent; 15–17 years, nil. Examination of sera from India indicated that all the types of ECHOvirus used in the serological tests (7–11) were spreading freely in children in that country. There are still many serological types of these viruses not yet described, e.g., of 261 strains of nonpolio virus isolated by Ramos-Alvarez in Mexico (65), 76 fell into one or another of ECHO Types 1–13, 6 were Coxsackie viruses, and 126 remained unclassified. Honig *et al.* (40) have observed a well-defined seasonal pattern of incidence of ECHO and Coxsackie viruses in the intestine, isolations from healthy children in West Virginia being almost confined to the months from June to October. In this study there was no indication that symptoms were associated with either ECHO or Coxsackie virus excretion.

There were moderately extensive outbreaks of aseptic meningitis in England and Western Europe during 1955 and 1956, from which a virus serologically identified as ECHO Type 9 was isolated with considerable regularity. The illness presented the usual signs of meningo-encephalitis of moderate severity with positive cerebrospinal fluid (C.S.F.) findings. In 20 or 30 per cent of the cases there was a conspicuous rash—blotchy pink or purplish macules on the face with often a rubelliform rash on the trunk. All ages contributed cases but the majority seen were aged 5 to 11. Recovery was complete in all (7, 15, 28, 69). Cytopathogenic viruses were isolated from faeces, throat washings, and stools and shown to be neutralized by ECHO Type 9 antiserum. A proportion of strains, however, were found to be pathogenic for suckling mice, and McLean & Melnick (56) report that they give rise to lesions resembling those produced by Coxsackie A strains.

Coxsackie virus infections.—It is now clear that Coxsackie B viruses are important causes of mild meningoencephalitis, symptomatically resembling nonparalytic poliomyelitis. Duncan *et al.* (23) have reported direct isolation on monkey kidney tissue culture of strains of Coxsackie B4 from the C.S.F. of three out of 33 patients with meningoencephalitis. From the same series of cases Beale *et al.* (4) isolated 13 strains of B4. Serological study of seven patients excreting B4 virus showed the development of specific antibody in six. McLeod *et al.* (57) have summarized the features of aseptic meningitis due to Coxsackie B viruses as seen in Toronto. They found no means of clinical differentiation from the other two common forms of virus meningitis and remark that the only diagnostic guide, apart from laboratory tests, is a knowledge of the current prevalence of paralytic polio, mumps parotitis, and pleurodynia in the community. In Toronto, B4 was current in 1952, B2 in 1954-55, and it is estimated that about 20 per cent of aseptic meningitis cases are due to Coxsackie virus infection.

As Sabin has pointed out (73), Coxsackie viruses resemble the other intestinal groups in being characteristically found in the young, in having a summer-fall seasonal incidence and in producing serological evidence of

immunity. To this may be added Taylor's (84) finding that in blood specimens from Egyptian children, Coxsackie viruses can be rather frequently isolated, A2, A6, and B2 having been identified. In South Africa, Wilkins *et al.* (89) reported meningoencephalitis resulting from Coxsackie B4 in association with an outbreak of Bornholm disease. In Johannesburg, Bayer & Gear (3) studied 75 cases of meningoencephalitis from which Coxsackie group A viruses were isolated from blood in one, from C.S.F. in three, and from faeces in 11 cases; Group B viruses, from blood in one, from C.S.F. in nine, and from faeces in 20. Most of these were B4 types.

Coxsackie viruses have been incriminated as a cause of acute myocarditis in infants. Papers by Montgomery and his colleagues (59) describe two small outbreaks in Johannesburg and in Southern Rhodesia. In the first, six of ten babies died after an acute febrile illness ending in circulatory collapse. The heart postmortem showed extensive focal myocarditis and Coxsackie B3 was isolated from brain and heart. In the Rhodesian episode, one of the three infants affected died with similar pathology. Coxsackie B4 was isolated from caecal contents on postmortem. Dekking (20) describes a case of fatal myocarditis from which Coxsackie virus was isolated in an infant whose mother had suffered from Bornholm disease a few days before delivery.

Diarrhoeal diseases—In a discussion of diarrhoeal disease in infants held in December, 1955, relatively little attention was paid to the possible part played by viruses. Hodes (39) reviewed the work in which infection had been conveyed experimentally to young animals, and Gordon & Whitney (33) that dependent on transmission to volunteers. The latter group includes (*a*) infectious hepatitis which, in infants, is frequently seen as a diarrhoeal syndrome without jaundice (9); (*b*) afebrile nonbacterial gastroenteritis (32); this has also been recognised in Japan; (*c*) febrile nonbacterial gastroenteritis, which appears to be immunologically distinct from the afebrile form (48). Other nontransmissible diarrhoeas occur and the status of these agents and the part they may play in infantile diarrhoea are both rather indeterminate. For a review see Gordon (31).

The part played by ECHOviruses in infantile diarrhoea is not yet clarified. Sabin (73) reports that Ramos-Alvarez found 24 of 56 rectal swabs from infants with diarrhoea yielded cytopathogenic agents in monkey kidney tissue culture. These included three poliomyelitis, three Coxsackie, two known ECHOviruses, and 12 unidentified viruses. The high level of such isolations suggests that some or all of these viruses can be responsible for infantile diarrhoea. More work will be needed to define which of them are significant in this respect.

Infectious hepatitis.—At the symposium on the laboratory propagation and detection of the agent of hepatitis in 1954, it was agreed that no one had established a satisfactory case for the propagation of the virus in tissue cultures, chicks embryos, or experimental rodents (83). Negative results were also reported in newborn swine and various primates. Much interest

has therefore been attracted to the claim by Rightsel *et al.* (66) that cytopathogenic agents have been cultivated from patients with clinical hepatitis on the Detroit 6 strain of cells in tissue culture. This strain of cells was developed from a sternal marrow biopsy from a patient with carcinoma of the lung; its cellular origin is uncertain. Like most strains of human cells capable of indefinite growth *in vitro,* the characteristic epithelial-type cell appeared after several passages *in vitro.*

Rightsel *et al.* (66) found that serum from a case of infectious hepatitis had a toxic effect on these cells and that the cytopathogenic effect was transmissible in series. Human amnion cells may also be susceptible but apparently do not allow continued passage. Evidence of neutralization by convalescent serum was also obtained. [From personal communications it seems that other workers are finding it difficult to reproduce these findings, although it is accepted that the Detroit work is convincing. A point of considerable interest noted in the Annual Report of the Virus Research Centre, Poona, India (86) is that specimens of serum from the 1955 Delhi outbreak of hepatitis sent to Detroit were found to contain virus. These were sent under code with other nonhepatic sera from which no virus was obtained].

The Arthropod-Borne Viruses

The name ARBOR, shortened "Arthropod-Borne," is coming into unofficial use for these viruses, of which well-known examples are responsible for yellow fever, dengue, and St. Louis and Western equine encephalitis.

The development of haemagglutination techniques, plus extensive work by laboratories in various parts of the tropics and subtropics, mostly under the aegis of the Rockefeller Foundation, has clarified relationships greatly in recent years. Groups are now defined primarily on a serological basis using haemagglutinin inhibition reactions. The groups so defined have other features in common and the classification is probably a natural one. The tropical regions are clearly the home of these viruses but extensions, similar to the historical invasions of yellow fever, reach subtropical and temperate regions. Table I lists the most important members by serological type and geographical distribution.

From the clinical point of view, another useful classification is made according to the epidemiological and clinical character of the disease when it involves populations other than those of a hyperendemic zone. Three types of clinical pattern can be recognised: I. Producing a high proportion of symptomatic generalized infections: Yellow fever, Dengue 1 and 2, West Nile, Chikungunya, Rift Valley fever and probably Venezuelan equine, Russian Spring-Summer, and Zika. II. Producing symptoms only in a small proportion of infections when the brain or other "target organ" is invaded: St. Louis, Western equine, Japanese B, Murray Valley. III. Producing haemorrhagic rash as well as general symptoms: Russian haemorrhagic fevers.

Perhaps the most interesting development in the last ten years has been

TABLE I

Serological type	America	Africa	India and S.E. Asia	Australasia
A	Western equine Eastern equine Venezuelan equine Mayaro	Semliki Chikungunya	?Chikungunya	
B	Yellow fever Dengue 2 St. Louis Ilheus	Yellow fever Dengue West Nile Uganda S Ntaya, Zika	West Nile Japanese B Dengue Russian S.S. ? Others	Murray Valley Dengue 1 and 2
C	Two groups from Amazon region			
Unclassified		Rift Valley fever Bunyamwera Bwamba		

the recognition that the clinical and epidemiological syndrome of dengue can be due to several different viruses. In addition to Dengue 1 (Hawaii) and Dengue 2 (New Guinea and Trinidad), some outbreaks of yellow fever may produce 50 per cent of infections with a mortality of one to two per cent only, with many cases clinically indistinguishable from dengue (51). Epidemics of West Nile virus infection in Israel have involved hundreds of cases with a clinical picture including virtually all of the features of dengue (6, 30). An extensive outbreak of a dengue-like disease in Tanganyika, East Africa, in 1952–53 (54), resulted in the isolation by inoculation of baby mice of a virus known from the native name of the disease as Chikungunya virus (68). The evidence seems adequate that this was responsible for the disease and it is therefore of great interest that the virus belongs to Casals' serological group A (11). Zika virus infection is serologically common in Africa and Macnamara (58) presents strong but incomplete evidence that this virus was responsible for an outbreak in Nigeria which, because of the occurrence of jaundice, was thought to be yellow fever.

From a review of the Russian literature by Gajdusek (*27*) it appears that the virus of Russian Spring-Summer encephalitis already known to be related to Louping ill virus of Scotland and tick-borne encephalitis of Central Europe (61) is responsible for haemorrahgic fevers in the Omsk and Bukovina regions. This would represent a further type of clinical manifestation.

The pathology of infection in this group of viruses thus appears to be derived from a primary viraemic phase which is common to them all. This phase is symptomatic or, at least, merges into a symptomatic phase of secondary viraemia in Group 1. Serious damage to the liver may be produced by yellow fever, Zika, and Rift Valley fever viruses. Most of the others produce clinically recognisable changes only when invasion of the central nervous system occurs in a small proportion of those infected. The incomplete evidence from Russia suggests that Russian Spring-Summer virus may be a versatile pathogen capable of producing a variety of secondary lesions.

There has recently been a growing interest in the possibility of using a combined approach to immunization within the Casals' Group B. Hammon *et al.* (35) showed that three children who had recovered from St. Louis encephalitis gave an excellent response to a Japanese B encephalitis vaccine, as against a minimal response by normal children. Among serologists there has been a recognition that, while a single infection with a member of Group B may give a relatively specific serological response allowing a presumptive serological diagnosis of the agent concerned, a second infection by a different member of the group usually provokes a high titre, broadly effective antibody response against all viruses of Group B. This was well shown in studies by Theiler (85) on a yellow fever outbreak in Trinidad where the patients studied included a number who had probably been infected by an Ilheus-type virus in the past. It has been suggested that immunization with standard yellow fever vaccine will provide sufficient immunity to allow safe and symptomless inoculation with living West Nile virus (64). This gives a wide antibody response which, it is reasonable to believe, might protect against any of the Group B encephalitis viruses, St. Louis, Japanese B, and Murray Valley encephalitis.

Other Virus Diseases

Cytomegalic inclusion disease.—It has long been recognized that the lesions associated with this disease closely resemble intranuclear inclusions found in the salivary glands of various rodents. Three groups of investigators have recently grown the responsible virus in tissue culture with production of typical inclusions in cell nuclei. Smith (79) obtained two strains, one from a localized salivary gland lesion, the second from a case of the generalized disease. Weller *et al.* (88) were able to isolate the virus from the urine of two cases in infants during life. Rowe *et al.* (71) recovered three strains by prolonged cultivation of human adenoid tissues. The virus grows on human fibroblasts but not on monkey kidney or HeLa cells. Serologically, the agents isolated by Smith and by Weller *et al.* are the same as those isolated by Rowe *et al.* About 20 per cent of human subjects show antibody to the virus (88).

Canine distemper virus antibodies in man.—An interesting and puzzling finding, now amply confirmed, is the presence of antibody against canine

distemper virus in a high proportion of children and adults in the United States of America (1, 49) and in Sweden (10). In both countries almost one hundred per cent of children show antibody by the time they are ten years old. Distemper virus has never been isolated from human beings and there is as yet no clear evidence as to the nature of the process by which the antibody is produced. It seems probable that it represents infection by some ubiquitous[2] virus serologically related to canine distemper virus. As far as we are aware, no comprehensive search for serological relationships between canine distemper virus and known viruses of human origin has yet been recorded.

Miscellaneous.—Gamma globulin derived from human beings bled 4 to 6 weeks after successful primary vaccination has been used for the prevention and treatment of complications of vaccination in infants, particularly eczema vaccinatum (Kaposi's eruption). Kempe *et al.* (50) report impressive results in this field and, on the basis of a small experience in India, consider that administration of hyperimmune gamma globulin, as well as immediate vaccination, will diminish the incidence and severity of smallpox in persons intimately exposed to the disease. Generalized or gangrenous vaccinia may be a manifestation of agammaglobulinaemia, so that administration of hyperimmune gamma globulin is indicated for two reasons. Similar work has been reported from Sweden (55).

[2] It is now clear that measles is responsible [Carlstrom, G., *Lancet*, **II**, 344 (1957); Imagawa, D. T., and Adams, J. M., *Federation Proc.*, **16**, 360 (1957)].

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DISEASES OF THE GASTROINTESTINAL TRACT[1]

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This effort to review the publications of the past year has been directed toward the field of fundamental research as well as those concerned with clinical problems. We have arbitrarily chosen, however, to emphasize certain subjects, such as investigations leading to a more thorough knowledge of the malabsorption syndrome, physiology of the small intestine, and chronic ulcerative colitis. A review of the liver, biliary system, and pancreas must be omitted because of limitations of space. Several books concerning the liver have appeared during the year (1 to 4). An issue of the *British Medical Bulletin* (5) presented a series of articles dealing with physiological, biochemical, and clinical aspects of liver disease, and the *Proceedings* of a four-day international symposium on basic aspects of liver physiology are due to be published shortly (6). Sherlock has reviewed the diagnosis and management of the jaundiced patient (7).

GASTRIC PHYSIOLOGY

Gastric secretion.—In the field of clinical physiology Hunt (8) has shown that duodenal ulcer patients produce approximately twice as much acid, chloride, and pepsin as normal subjects, while Rovelstad (9) has produced similar results concerning acid by making continuous records of intragastric and intraduodenal pH in ulcer patients. Cooper & Knight (10) concluded, as a result of a series of acute experiments, that cigarette smoking did not affect gastric acid production in duodenal ulcer patients, but both smokers and nonsmokers were included in the control group and whether inhalation was consistently practiced is not stated. Marks (11) has studied acid production following partial gastrectomy, using a balloon to occlude the stoma, and has found that patients who subsequently developed jejunal or stomal ulcers had high postoperative acid levels.

Gastric motility.—Woodward *et al.* (12) have shown that chemical stimulation of the antrum does not affect gastric motility, whereas, mechanical stimulation causes an increase. Lorber & Shay (13) have demonstrated an inhibiting effect on gastric motility when isotonic hydrochloric acid, 25 per cent glucose with 5 per cent sodium bicarbonate, and olive oil are placed in the duodenum. As the olive oil effect has a larger latent period, they suggest that it may be mediated via an humoral agent, whereas, the first two are probably mediated via a short reflex arc. Schapiro & Wood-

[1] The survey of the literature pertaining to this review was concluded in July, 1957.

ward (14) have shown that although obnoxious odors will abolish appetite, they have no effect on gastric or duodenal motility, while Stunkard & Wolff (15) feel that hunger contractions were abolished by the administration of 50 per cent glucose intravenously. Booth *et al.* (16) found no difference in the ratio of gastric emptying between healthy men and women. Nor did Hunt (17) find any significant difference in the speed of emptying between normals and duodenal ulcer patients. On the other hand, Smith *et al.* (18) did find that intraluminal pressure wave activity was increased in duodenal ulcer patients both during the emptying of an acid meal and also during bouts of pain. Newer anticholinergics (19, 20) have been shown to inhibit gastric motility while BZ55 causes an increase (21). Morphine sulphate apparently initially stimulates gastric motility and later depresses it (22).

Gastric histopathology.— Aside from gastric cytologic study in the diagnosis of gastric neoplasia, scant attention has been paid to gastric histopathology during the past year. Two articles of interest are those of Siurala (23) and Morson (24). The former points out the practicality of intracellular lipase determinations by histochemical techniques first outlined by Gomori. Morson re-emphasizes the relationship of so-called "intestinalization" of the gastric mucosa and the development of gastric carcinoma.

ESOPHAGUS

A symposium on the esophagus and its disease in the February, 1957, issue of the *American Journal of Surgery* (25) provides an excellent review of a wide variety of esophageal problems, as do the *Proceedings of the 1956 International Congress of Gastroenterology,* published separately, and in *Gastroenterologia,* Volume 86 (26, 27).

Physiologic studies have been concentrated on the gastroesophageal junction. Fyke, Code & Schlegel (28), by means of intraluminal pressure studies, have shown a high pressure zone between the low positive pressure zone of the stomach and the negative pressure zone of the esophagus. This high pressure zone reached from 1 to 2 cm. below to 1 to 2 cm. above the diaphragmatic hiatus, and disappeared during early swallowing to reappear as the primary peristaltic wave passed through the area. Botha, Astley & Carré (29) show by means of combined cineradiography and pressure studies that the high pressure zone may be either above or below the diaphragm and conclude that this sphincter is separate from the diaphragm.

STOMACH AND DUODENUM

Duodenal Ulcer

Medical treatment.— A review of medical management of duodenal ulcer over the past year reveals a striking lack of scientific attempts to assess accurately the effects of newer drugs and methods of treatment by means of controlled trials and statistical analyses. In most cases, concrete opinions are expressed on the basis of clinical impressions. In a disease of such frequent occurrence as duodenal ulcer, it should not be difficult to

organize "double blind" clinical trials of antispasmodics and alkalis, thereby obtaining more definite evidence as to the ability or failure of newer preparations to benefit the patient.

Diet.—Winkelstein (30) reports a favorable response in 87 per cent of refractory peptic ulcer patients following the use of a high protein, high calorie powder, but no controls were used. Kleeberg (31) has been impressed with the value of sweet dried almonds in ulcer patients, while Dekkers (32) advocates a high carbohydrate diet. He feels that dietary protein is a strong stimulus for acid secretion and in his uncontrolled series 83.7 per cent of patients became asymptomatic.

Antacids.—Dihydroxy aluminum amino acetate (D.A.A.) was first prepared in 1944, and recently fresh views of its usefulness in peptic ulcer disease have been put forward by Berry *et al.* (33) and Rider *et al.* (34). It achieves equilibrium with acid more quickly than aluminum hydroxide and in 2 gm. doses will produce anacidity lasting up to 45 min. In the two uncontrolled series, results following its use were excellent in 100 per cent and 87.7 per cent of cases, respectively.

Anticholinergics.—Two adequately controlled trials of newer anticholinergics have been reported. In a series of 563 patients, Atwater (35) found that methantheline bromide (Banthine) and tridihexethyl iodine (Pathilon) were more effective than a placebo or atropine in relieving mild symptoms, but were no more effective in the relief of severe sypmptoms of patients with peptic ulcer. The recurrence rate was high, but significantly less in the methantheline and tridihexethyl iodine group, and he considered that anticholinergics did little to alter the basic course of the disease. Cayer (36) studied the effects of anticholinergics in the incidence of recurrences and he found that although patients on methantheline or propantheline bromide (Pro-banthine) had more relief of symptoms as compared with patients on atropine or a placebo, there was no significant difference in the incidence of recurrences. He, too, felt that the newer anticholinergics do little to affect the natural history of duodenal ulceration, although they may be helpful in symptomatic treatment. Glass & Rich (37) conclude that a new antispasmodic derived from mandelic acid is effective in the prevention of recurrences, using the recurrence rate in previous years as a control, while Barowsky *et al.* (38) report favorable symptomatic results following short-term intensive anticholinergic therapy, using the past history of the patient as a control.

Various reports of uncontrolled trials of other anticholinergic drugs have appeared over the past year. The consensus is that all these drugs are quite effective in the relief of symptoms of peptic ulcer disease, but a comparative assessment of their merits is not possible on the results of isolated uncontrolled trials. Drugs investigated include penthienate bromide (Monodral Bromide), (39); 1-methyl-3-benziloyl-oxyquinuclidinium bromide (Marplan), (40); tricyclamol chloride (Elorine Chloride), (41); methscopolamine bromide (Pamine), and diphemanil methyl sulphate (Prantal) (42); and propantheline bromide (Pro-banthine), (43).

Despite the demonstration by Kirsner & Ford (44) that reserpine is a potent stimulus of gastric secretion, Drenick (45) has used the drug in the treatment of ambulatory patients with peptic ulcer disease apparently with some benefit. Hollander (46) has tried the effect of acetazolamide (Diamox) as an inhibitor of gastric acid secretion, but has found it to be not sufficiently strong for clinical usefulness. Levin *et al.* (47) have described further follow-up experiences with gastric irradiation in the treatment of duodenal ulcer. To date, 723 patients have been so treated and followed for a period from five to eighteen years. Both the severity and incidence of recurrence has been greatly reduced following treatment, as has the incidence of hemorrhage and perforation. Nine patients have died of malignant disease arising in the irradiated area, four from gastric carcinomata, four from pancreatic carcinomata, one from heptic carcinoma (this patient had cirrhosis), but so far there have been no deaths from leukemia. Further observation of these irradiated patients should be interesting.

Duodenal Biopsy

A stimulus to the study of duodenal cellular physiology and biochemistry has resulted from the development of small bowel biopsy tubes (48, 49). The procedure has been shown to be safe in the experiences of Shiner and of Crosby. The writers' experience in over thirty biopsies further confirms the safety.

Of interest are the reports of Milton & Smith (50) and Milton, Smith & Armstrong (51) dealing with duodenal physiology. They refer to the theory first proposed by Keith in 1915 that the frequency of contraction of the small bowel is under the control of pace-makers similar to the sino-auricular and atrioventricular nodes of the heart. Evidence is presented to show that one of these pace-makers is located in the duodenal wall near the bile duct.

Gastric Ulcer

Very little advance in our basic understanding of the process of gastric ulceration has been made during the past year. The argument as to whether benign ulcers undergo malignant degeneration continues to occupy a prominent place in many articles. The pendulum seems to be swinging toward those who believe that an ulcer is either benign or malignant to begin with and that a benign ulcer rarely, if ever, becomes malignant (52, 53). The old adage that an ulcer on the greater curvature of the stomach is always malignant continues to be contested in a number of reports. It seems well-established that the percentage of greater curve ulcers of the malignant type is high, but by no means 100 per cent (54). Although attempts have been made to distinguish ulcers in the pyloric canal from those at other gastric sites on the basis of atypical symptomatology, the constancy of these atypical signs has been questioned by some authors (55). The precise role of the pituitary-adrenal gland mechanism in the production of gastric ulcers remains obscure although so-called "stress ulcers" continue to be reported (56, 57). There is a unanimity in these reports in so far as the lack of back-

ground and prodromata in the development of these ulcers is concerned. The first symptom frequently is that of perforation or bleeding. Another syndrome which seems to be rather characteristic and of sufficient atypicality from the usual benign gastric ulcer to warrant separate comment is the large, indurated gastric ulcer occurring in the aged (58).

Cytologic examination of the gastric contents has become increasingly recognized during the past year. Reports prior to the past year (59, 60) have indicated that simple gastric lavage employing a buffer solution and chymotrypsin play an invaluable supporting role in the differentiation of benign and malignant lesions (61).

A well-conducted survey of the problem of postgastrectomy tuberculosis indicates that active tuberculosis becomes worse after gastric resection. There is, however, no proof that gastric resection leads to increased susceptibility to tuberculosis or to reactivation of old tuberculosis (62).

Recent advances in the use of fine glass fibers for the production of a completely pliable "fiberscope" opens the possibility of endoscopy unhampered by loss of visibility due to sharp angulation in the gastric antrum, pylorus, or duodenum (63, 64).

The basic medical regimen for the treatment of gastric ulcers remains unchanged. It consists of multiple feedings, antacids, anticholinergics, varying degrees of sedation plus superficial psychotherapy, and the establishment of rapport between the patient and physician. Like the medical program, surgical therapy is unchanged. Subtotal gastrectomy (70 per cent without vagotomy or 50 per cent with vagotomy) continues to be the operation of choice.

Gastric Hemorrhage

Etiology.—One problem of concern to the reviewers relative to the etiology of gastric hemorrhage is whether or not the ingestion of salicylates has any accurate basis for being a causative factor. Kelly (65) reports on three patients who noticed melena consistently related to episodes of headaches which were treated with acetylsalicylic acid. Hypoprothrombinemia was not the cause of the bleeding, as the prothrombin time was normal in all the patients in whom it was determined. He then examined the hospital records of 49 patients with unexplained upper gastrointestinal bleeding and found that 32 per cent of these patients had received salicylate therapy for such conditions as severe headache, arthritis, etc., after which the bleeding occurred. We agree with him that all patients with upper gastrointestinal hemorrhage should be questioned regarding the use of salicylates and concede that it possibly is an occasional causative factor. However, the last patient seen by the writers whose bleeding was thought to result from salicylate therapy was found to have a carcinoma of the duodenum.

Recent experiences with severe gastrointestinal hemorrhage occurring in individuals with gastroenteric stomas caused Mydland *et al.* (66) to make a survey of their own patients. Gastrojejunitis or gastrojejunal ulcer was responsible for the hemorrhage in 72 of the 100 patients who had previously had a gastroenterostomy. There were other suspected causes, such as un-

healed gastric and duodenal ulcers, erosive gastritis, and jejunogastric intussusception. It is interesting to find that in this group, 35 per cent of the patients were classified as having had severe hemorrhage and beyond this, 45 per cent of the patients had their hemorrhage ten or more years after their gastroenterostomy.

Vandenbroucke (67), in analyzing a series of 137 patients with severe hemorrhage of the esophagus, stomach, and duodenum, found that the hemorrhage was due to gastric carcinoma in nine patients, ulcer of the stomach in 14, duodenal ulcer in 48, and portal hypertension in 27. Other lesions included pulmonoesophageal fistula, periarteritis nodosa and duodenal ulcer, carcinoma of the pancreas, angioma of the stomach, hiatus hernia, hemorrhagic gastritis, and carcinoma of the gallbladder. Hemorrhagic diathesis, interestingly enough, rarely seems to be responsible for severe hemorrhages of the upper gastrointestinal tract. In 18 per cent of these patients the origin of the severe hemorrhage was not found. Throughout the literature, the figures on this generally range from 10 to 25 per cent.

As emphasized by Kirtley *et al.* (68) there is general agreement that peptic ulceration is responsible for most instances of bleeding when the site is not determined. For this reason, they recommend empiric gastric resections for unexplained bleeding. Such a procedure was performed on 21 of 26 patients with obscure upper gastrointestinal bleeding in the belief that the results in these 21 cases appear to substantiate the validity of subtotal resection of the stomach when no definite cause of bleeding is found.

Therapy.—Snapper (69), in a discussion on this subject, expresses the views of the authors very effectively, and we should like to quote from his discussion:

"About twenty-five years ago Sir Arthur Hurst published his statistics which showed that only less than 3 per cent of his patients with upper gastrointestinal hemorrhage died. At that time the blood transfusion was just being introduced into the practice of medicine and only small amounts of blood were given. Thus, any method which leads to a fatality in upper gastrointestinal hemorrhage exceeding 3 per cent should be looked at askance."

Snapper goes on to comment that

"A patient with an ulcerating hemorrhage should be kept in bed, should not be carried around too often, should either receive milk diluted with lime water or occasionally a Meulengracht diet. The amount of blood given should be limited and should not exceed the quantity which is necessary to keep the patient out of shock. When every patient with an upper gastrointestinal hemorrhage must receive so much blood that the hemoglobin climbs to 10.0 grams per cent or higher and the systolic blood pressure to 120 mm. of mercury or higher, then the danger for continuous hemorrhage is markedly increased. This hypervolemia causes hemorrhage as soon as a weak spot in the circulatory tree is present anywhere. In other words, if the fatality of upper gastrointestinal hemorrhage exceeds 3 per cent, iatrogenic or chirurgogenic influences are to be blamed."

Our own interest has followed the lines of developing means with which to determine efficiently the blood volume and thereby prevent the hy-

pervolemia mentioned by Snapper. Tibbs (70), in a discussion on blood volume and gastroduodenal hemorrhage, studied the accuracy of the Evans blue dye and the hematocrit method of estimating the blood volume and compared this with the combined results of the measurement of plasma volume with the Evans blue dye and the red cell volume with radioactive phosphorus in patients with uncomplicated peptic ulcer and in others with gastroduodenal hemorrhage. A group of 33 patients with gastroduodenal hemorrhage of different ages and of either sex were studied. The clinical signs in these patients were related to their blood volume and the results were recorded. He emphasized that the pulse rate, if raised, can often give positive guidance, but that a slow pulse rate may give an erroneously favorable impression. The systolic and diastolic pressure, if low, gives positive guidance. In middle-aged and elderly patients the blood pressure may remain deceptively high in spite of reduction in blood volume because of pre-existing hypertension. Pallor of the hands indicates a great likelihood of deficient blood volume and extreme pallor makes deficiency a certainty. The value of the hemoglobin, temperature of the extremities, sweating, venospasm, respiratory rate, and return of skin color after blanching by pressure is evaluated. With all of this information he then suggests a program for the proper time to administer a blood transfusion.

It is interesting to observe the change which has taken place in the therapy of massive gastric hemorrhage over the past 28 years as outlined by Mixter *et al.* (71). During the years 1928 to 1937, they treated 135 patients without operation, with a mortality of 12 per cent. From 1937 to 1942, 142 patients were treated, 104 by conservative measures with two deaths, 24 by operation with one death, and 14 were subjected to emergency operation with 35 per cent mortality. There was an over-all mortality of 5.6 per cent. From 1942 to 1945, 42 additional patients were treated, 75 per cent by known operative methods with a mortality of 25 per cent. Since that time, 32 additional cases have been treated with a surgical mortality of 44 per cent and a medical mortality of 29 per cent. From these statistics, the group concluded that when the source of bleeding is obscure and the administration of blood fails to change the hypovolemic picture promptly, the patient must be explored before his condition becomes too serious.

An interesting report from Stockholm by Aldman & Wallensten (72) concerns a study of 3879 patients with peptic ulcer, 511 of whom presented manifestations of hemorrhage. This study extended over the period from 1942 to 1953. Twenty-three died, a mortality rate of 4.5 per cent. Their conclusion is that in the case of massive hemorrhage the blood should be replaced as fast as possible and if, in spite of this measure the bleeding does not stop and the life of the patient is in danger, surgical intervention should be considered and performed as soon as possible after the onset of hemorrhage, especially in patients over 60 years of age. It should be realized that some deaths may follow relatively mild hemorrhage, indicating that the hemorrhage itself as emphasized by Smythe *et al.* (73) did not cause death, but initiated events that ended fatally. Two of the 15 deaths in their group

resulted from hepatic coma and a third from pulmonary embolism. They emphasize that the much higher death rate (15 of 40) in patients whose bleeding was not caused by peptic ulcer shows that conclusions drawn from data on results in patients bleeding from peptic ulcer cannot be applied to those with hemorrhage from other causes. Age and liver disease present the greatest hazard to these patients. Bleeding seems to be only an initiating factors in the downhill course of patients with cirrhosis.

Another report by Ungeheuer (74) from Stuttgart, Germany, indicates that of 125 patients with peptic ulcer who were operated upon because of massive gastric hemorrhage, 11 (8.8 per cent) died. Of 51 patients who were operated upon early, that is, 24 hr. after the onset of bleeding, two (3.9 per cent) died. His thinking is that medical treatment does not banish the risk of recurrence of the ulcer or hemorrhage, nor does it eliminate the possibility of perforation or a malignant degeneration, whereas, the beneficial results of surgery are more likely to be permanent.

One item which should be mentioned is the incidence of homologous serum jaundice following transfusion. The figure remains somewhere between 1 and 2 per cent.

Sachs (75) presents an outline for management of bleeding from esophageal varices by the utilization of the Sengstaken or similar triple lumen double balloon tube, as follows: Inflate the lower balloon with 150 to 300 cc. of air. A one-pound traction should be applied to the balloon. Inflate the upper balloon to 20 to 30 mm. of mercury, which should stop the bleeding. Maintain the pressure in both balloons. Aspirate through the tube and, likewise, feed through it. If bleeding continues, then the patient is obviously bleeding from below the esophagus. After 12 to 24 hr. gradually deflate both balloons to forestall mediastinitis. Then start feeding the patient.

Gastric Carcinoma

In 1903 the National Office of Vital Statistics reported a death rate of 25.1 per 100,000 population from cancer of the stomach and liver. Fifty years later, in 1953, as reported by Myers (76) there is a death rate of 21.4 from the same disease. It should be realized that this includes the liver, as well as the stomach. Other reports give an even more optimistic decrease in incidence of gastric cancer.

Of considerable interest in the field of genetics is the report by Yates *et al.* (77) of two fatal cases of carcinoma of the stomach in monozygotic twin women, aged 66 and 67, in whom the tumor was apparently present simultaneously, although the symptoms began and the deaths occurred nearly a year apart. Both cancers were adenocarcinomas arising in the gastric mucosa. An exploratory laparotomy was performed in each patient and revealed extensive neoplasm of the stomach that was not resectable.

Another interesting relationship relative to the ABO blood-groups and gastric cancer has been studied by Billington (78). He analyzed the records of four hospitals affiliated with the University of Sydney for the years 1947 to 1954. No over-all association was found between blood group A and

cancer of the stomach in the Sydney population, whereas, a report from the United Kingdom in 1953 has shown such an association. When gastric carcinoma was divided in its relationship to the ABO blood group system according to the site of the three types of gastric glands, prepyloric and cardiac lesions were significantly associated with blood group A, and body and fundus lesions with blood group O. Possibly the differential localization of gastric carcinoma and its relationship to the ABO blood group-gene system may be of importance in the epidemiological study of gastric cancer as a whole. Jennings *et al.* (79) have also made a study of the relationship of cancer of the stomach to ABO blood groups. They analyzed the records of 131 patients subjected to partial or total gastrectomy for stomach cancer in a five-year period. Their conclusion is that there is a 70 to 49 ratio in the blood groups A to O. The antral mucosa is more often inflamed in group A and inflammation and cancer are more common in this group than among persons having blood group O.

Factors involved in screening patients for gastric cancer are a continuing source of concern. Such a study has been reported by Hitchcock (80) in which he indicates that 80 per cent of patients with gastric cancer have complete achlorhydria following triple histamine stimulation of the gastric mucosa. In their study of 7786 men and women, 20 cancers were present. In this group there were four patients who developed cancer after once having had a negative gastric x-ray in 24 months, 50 months, 63 months, and 64 months. Of the 75 per cent of the patients seen in their cancer detection clinic who were normal as far as gastric secretion is concerned, there has been no indication of a gastric carcinoma developing during the eight years and three months period of follow-up. In the asymptomatic group of patients there were three (30 per cent) who had positive lymph nodes at surgery as contrasted to 10 (91 per cent) in the symptomatic group. In only 10 per cent of their patients with polyps were the polyps found to be malignant. One person out of 357 examined at their cancer detection center had a gastric cancer. Individuals who had pernicious anemia or were achlorhydric and over the age of 50 years have a 490 per cent greater chance of developing gastric cancer. Pernicious anemia patients have a 21.3 times greater chance of developing gastric cancer.

Treatment.—The results of treatment of gastric cancer as outlined by Olsson *et al.* (81) are on a surgical basis. If the cancer is operated upon before it is spread outside the stomach, the prospects of a cure are not so poor as widely supposed. Thus, in their material, 31.5 per cent of the patients without visible metastasis survived the operation for more than five years. The occurrence of metastasis should, however, not contraindicate surgery. In 5.4 per cent of such cases the patients lived for more than three years after operation. Walters (82) in his report mentions an interesting feature relative to total gastrectomy to the effect that the risk is too high and the results not improved by using total gastrectomy in preference to partial gastrectomy when the latter could be performed by going well beyond the lesion. Beal & Hill (83) evaluated their surgical treatment of

the cancer of the stomach and presented some rather optimistic findings. They, too, feel that the efficiency of total gastrectomy cannot be adequately assessed on the basis of available information.

Clinical and pathophysiological problems of total gastrectomy in patients with cancer of the stomach have been evaluated by Lindenschmidt (84) in Germany, and Binda (85) in Italy. Their reports are largely statistical, based upon their operative results. However, they, too, emphasize that in the postoperative period adequate administration of proteins, fats, parenteral iron, vitamin B_{12}, and folic acid are indicated.

Sarcomatous tumors of the stomach as reported by Eker (86) comprised 1 to 8 per cent of malignant tumors of the stomach. Prognosis for gastric sarcomas is claimed to be considerably better than for gastric carcinomas. In their own series of 26 patients operated upon for sarcomatous tumors of the stomach, 20 patients are alive and without symptoms after five years or more. Rauber *et al.* (87), however, reported a much more discouraging situation with reticulosarcoma of the stomach in their series of patients, since no patients survived longer than 15 months.

Finally, Tesler *et al.* (88) reported two cases, one a white male, aged 63, with an adenocarcinoma operated upon in 1943, whose last x-ray obtained in May, 1954, showed no intrinsic defect of the stomach, and the other a white male, aged 65, with a subtotal gastrectomy performed in June, 1947, and whose last x-ray obtained in February, 1955, showed no evidence of malignant infiltration.

Small Intestine

Absorption tests.—Absorption techniques have continued to receive considerable attention. Ruffin *et al.* (89) have shown that in normal patients after administration of I^{131}-labeled triolein an average of 14 per cent of administered radioactivity was found in the blood stream 3 to 6 hr. after the test meal and only 1 to 2 per cent of ingested radioactivity was excreted in the stool. Patients with functional gastrointestinal disturbances showed normal values while patients with pancreatitis averaged blood levels of 8 per cent and stool excretion of 19 per cent of ingested radioactivity. Carcinoma of the pancreas, sprue, Whipple's disease, and regional enteritis led to greater abnormality. Cirrhosis and ulcerative colitis were accompanied by low normal absorption, while after subtotal gastric resection or vagotomy plus gastroenterostomy, blood levels and fecal losses of radioactivity were comparable to those seen after pancreatitis.

The evaluation depends on averages and does not give information concerning the spread of values or comparison of the results of this test with those of other tests of intestinal absorption. In a subsequent article, the same group (90) presents more detailed data concerning absorption of I^{131} triolein in patients with pancreatic disease. Seven of eight patients with pancreatitis and eight of ten patients with carcinoma of the pancreas showed strikingly abnormal fecal loss of I^{131} while the three remaining cases were within normal limits. Blood levels of I^{131} were abnormally low in 10 of 12

with pancreatitis and in 16 of 18 cases with carcinoma of the pancreas.

As with Ruffin's group, Beres, Wenger & Kirsner (91) depend primarily on blood levels of I^{131}, but measure only the protein-bound lipide fraction of blood radioactivity. They present data showing fair correlation of 24-hr. urinary I^{131} excretion with fat excretion by traditional balance techniques and good correlation of fecal I^{131} excretion with chemical fat balance. The blood levels are presented as averages for each disease state without ranges or correlations with fecal fat. They prefer to use the blood radioactivity levels because of the greater simplicity and absence of need for complete urine or stool collections.

McKenna, Bourne & Matzko (92) measured radioactivity in blood, stool, and urine after ingestion of I^{131} triolein. They found the blood levels of I^{131} an unreliable index of absorption, blaming this on variation in gastric emptying time. Their data show considerable overlap between the curves of normal and abnormal patients. They state that fecal excretion of I^{131} correlates well with the results of chemical balance studies although detailed data are not presented to show this.

Since fatty acid is theoretically absorbed without need of digestion, a comparison of I^{131}-oleic acid absorption with that of I^{131} triolein has been used by Malm, Reemtsma & Barker (93), and by Isley *et al.* (94). Patients with primary or secondary sprue absorbed both substances poorly while patients with pancreatic insufficiency absorbed oleic acid well and triolein poorly. An exception was noted by Reemtsma *et al.* (95) who found that seven patients with fibrocystic disease of the pancreas showed not only poor triolein absorption, but also moderate impairment of oleic acid absorption. They postulate a generalized absorptive defect, as well as a pancreatic secretory defect in these patients.

Sandweiss & Levy (96) using I^{131} oleic acid and S^{35} methionine found increased fecal losses in patients with ulcerative colitis. Although not in the strikingly abnormal range found in sprue, active ulcerative colitis was accompanied by fecal excretion twice as great as normal and there was no overlap between normal values and those found in active ulcerative colitis. Absorption improved as the disease became less active.

Gardner & Santiago (97) and Benson *et al.* (98) advocate use of the *d*-xylose absorption test. They found that 5 hr. urine collections separate normal from abnormal patients better than blood curves. Oxenhorn, Estren & Adlersberg (99) recommend the urinary excretion of Co^{60}-vitamin B_{12} as a good test of malabsorption while Glass & Laughton (100) prefer to measure hepatic uptake, showing that repeated doses of Co^{60}-vitamin B_{12} lead to comparable increments of radioactivity in the neighborhood of the liver when measured six to seven days after each successive dose. Thus, comparison of the effect of parenteral doses and of oral feeding with and without intrinsic factor can be used to separate sprue, in which oral B_{12} is not absorbed under any circumstances, from pernicious anemia in which the addition of intrinsic factor leads to good absorption of Vitamin B_{12}.

Wenger, Kirsner & Palmer (101) show that plasma carotene levels provide a good screening test for steatorrhea. As in their I^{131} triolein studies, they present comparisons with fat balance studies which show that the test is not infallible since seven patients with steatorrhea showed normal carotene levels, but the test probably compares well with those discussed above. In most of these studies there is a striking tendency to emphasize that on the average, values in malabsorption syndromes are different from normals. A few studies have provided data from individual cases to show how much overlap there is between clinically normal and abnormal patients, but only the Chicago group has consistently depended upon a comparison of individuals rather than upon averages between the basic index of malabsorption, fat balance studies, and the new test under evaluation.

Malabsorption syndromes.—Small bowel biopsy instruments which can be passed by mouth have been described by Shiner (102) and by Crosby & Kugler (103). Biopsies performed with the Shiner tube in patients with nontropical sprue show in most, but not in all cases, atrophy and clubbing of the villi, while patients with pancreatic or postgastrectomy steatorrhea show normal mucosa (104). This confirms that the earlier postmortem findings of Adlersberg & Schein (105) now extended to 11 patients by Himes & Adlersberg (106) were indeed typical of sprue and not the result of postmortem change.

Gardner has continued his studies of tropical sprue in Puerto Rico, showing that gastric washings in sprue patients contain the same large cells found in pernicious anemia (107). He also found that both mucoprotein and mucoproteose as measured by the method devised by Glass and Boyd are reduced in stomach and jejunal contents in sprue (108), and that jejunal contents of sprue patients do not contain bacteria any more frequently than do normals (109). This last observation is, of course, not conclusive since only the jejunum was sampled and it is possible that ileal flora may be significantly altered. French, Gaddie & Smith (110) support the view that the bacterial flora plays an important part in tropical sprue with the observation that all of seven British soldiers with tropical sprue responded rapidly to broad spectrum antibiotics, including nonabsorbable sulfonamides, streptomycin, chlortetracycline, and chloramphenicol. Sammons, Vaughan & Frazer (111) have further complicated this problem by their isolation from a patient with steatorrhea of a *Streptococcus fecalis* strain which synthesizes large amounts of fat (30 mg. in four days from 10 ml. of medium).

A symposium on the malabsorption syndrome fills an entire issue of the *Journal of Mt. Sinai Hospital,* New York (112) and discusses the clinical picture of nontropical sprue in great detail. Gardner (113) and Perez-Santiago & Butterworth (114) describe the clinical appearance of tropical sprue in Puerto Rico.

Finlay & Wightman (115) present results of steroid therapy and gluten-free diet in 15 patients with primary sprue and 12 with secondary sprue. Steroid therapy resulted in a more rapid, but less complete response than

did the gluten-free diet. The combination of both steroid therapy and gluten-free diet was superior to either one above. A striking finding was that five of seven patients with secondary sprue responded well to the gluten-free diet. If this is confirmed it is strong evidence against the theory that primary sprue represents gluten allergy and suggests that gluten may have a nonspecific effect demonstrable in anyone with decreased absorptive ability.

Malignant carcinoid.—Malignant carcinoid has continued to stimulate interest. MacDonald (116) found that 59 per cent of 356 carcinoids were appendiceal, with ileum, jejunum, and stomach the next most common sites. About 50 per cent of extraappendiceal carcinoids were invasive while about 10 per cent showed metastases in contrast to the appendiceal carcinoids which were invasive in 10 per cent and metastasized in 0.5 per cent of cases. Of 21 cases with widespread metastases, nine showed diarrhea, eight peptic ulcer, a complication not previously emphasized, while four showed the full carcinoid syndrome with diarrhea, episodic flushing, and skin rash. Two patients showed isolated pulmonary stenosis and two bronchoconstriction.

Pernow & Waldenström (117) and Sjoerdsma *et al.* (118) have added further cases to their previously reported series of patients with the malignant carcinoid syndrome, stressing that the diversion of tryptophan into the formation of 5-hydroxytryptamine by the tumor may result in tryptophan deficiency. Both Sjoerdsma's group and Cole & Bertino (119) found partial relief from diarrhea, nausea, and flushing in the carcinoid syndrome in the administration of chlorpromazine 25 mg. q. 6 hr. In Bertino's case urinary excretion of 5-hydroxyindoleacetic acid was reduced by chlorpromazine therapy and increased when therapy was stopped.

Studies of 5-hydroxyindoleacetic acid excretion in a variety of diseases by Haverback, Sjoerdsma & Terry (120) showed increased excretion only in the carcinoid syndrome. Boyland, Gasson & Williams (121) did find slightly elevated bloods levels of 5-hydroxytryptamine, 5-hydroxyindoleacetic acid, and indoleacetic acid in carcinoma of the larynx and bronchus. These levels were well below those found in the carcinoid syndrome.

Miscellaneous small intestine lesions.—The Peutz-Jeghers syndrome of familial intestinal polyposis with mucocutaneous melanin pigmentation was reviewed by Bartholomew, Dahlin & Waugh (122) who report six cases, and by Dormandy (123) who reports 21 cases. Both emphasize bleeding and intussusception as presenting complaints.

Crohn, Yarnis & Korelitz (124) discuss the relationship of regional enteritis and pregnancy. Pregnancy frequently activated enteritis, particularly if no prior therapeutic surgery had been performed. Many of those whose enteritis was active during pregnancy improved only to get worse again postpartum.

Morlock, Goehrs & Dockerty discuss primary nonspecific ulcers of the small intestine on the basis of 32 cases, emphasizing bleeding and intestinal obstruction as presenting complications (125).

LARGE INTESTINE

Chronic Ulcerative Colitis

Etiology.—Little fresh light has been shed on the etiology of this condition, although the discovery by Melrose (126) of a varying European incidence may ultimately be of significance in this respect. On the basis of histochemical studies on rectal biopsy specimens taken from normal subjects and patients with ulcerative colitis, Streicher *et al.* (127) support the theory that ulcerative colitis may be a connective tissue disease akin to periarteritis nodosa. They found that even normal subjects showed a significant degree of interstitial edema and cellular infiltration of the rectal mucosa (an indication of the unstable state of the lower bowel), while ulcerative colitic specimens showed thinning or absence of basement membranes of surface epithelium, glands, and blood vessels, together with diminution and possibly faulty production of mucus and less of granularity of subbasement-membrane fibroblasts. Another possible, though admittedly rare, provoking factor is suggested by Lumb & Protheroe (128) who describe four of 57 cases of diverticulitis which progressed to frank ulcerative colitis. In comparing the pathology of the two conditions they point out that diverticulitis is characterized by localization of the lesion and an absence of complete crypt destruction (thereby allowing normal regeneration to occur), whereas, the opposite is seen in ulcerative colitis. They feel that these two differential features may have some bearing on the increased incidence of carcinoma in ulcerative colitis. Analysis of ABO blood groups in 134 patients (129) showed a normal distribution as compared with blood donor controls. Studies of blood group secretor status might conceivably yield more interesting results.

Pathology.—Lumb (130) has studied 271 rectal biopsy specimens removed from 236 patients. The earliest signs of activity are seen at the base of the crypts with poor staining, vacuolation, and nuclear degeneration of the basal cells. Progression leads to the formation of small erosions and later to crypt abscesses which may coalesce and strip off the overlying mucosa. He does not mention periarteritic-like lesions which, according to Ihre (131), are seen in 5 per cent of patients with chronic ulcerative colitis. A comprehensive account of ileal lesions found in patients with ulcerative colitis is given by Counsell (132) on the basis of a study of specimens removed at operation. Back-wash ileitis was seen in 18 of 107 specimens while three examples of regional ileitis were found in 120 patients with ulcerative colitis. It is interesting to find that in only four of the patients with back-wash ileitis was the condition suspected as a result of preoperative x-ray examination. Ileostomy ileitis is discussed, stress being laid on the fact that the condition results from subacute obstruction of the ileostomy rather than from retrograde spread of the primary disease process. Bendandi (133) has studied liver function as reflected by standard laboratory tests in 190 cases of chronic ulcerative colitis. Various flocculation tests were abnormal in 20.3 per cent (colloidal gold) to 45.4 per cent (zinc sul-

phate) of patients, while serum bilirubin, alkaline phosphatase and urinary bile tests were consistently negative in patients without clinically evident liver disease.

Natural history and prognosis.—Several large series have been reviewed, in order to determine the natural history and prognosis (134 to 137). Banks *et al.* (134) report a particularly good follow-up of 244 of 255 patients for an average of 12.1 years. After that average period approximately 20 per cent were perfectly well, 20 per cent had mild symptoms, 20 per cent had serious symptoms, 17 per cent were asymptomatic after surgery, 3 per cent had malfunctioning ileostomies, while 20 per cent were dead. All agree on the poorer prognosis associated with total colonic involvement or severe constitutional symptoms, while Flood *et al.* (137) report a similarly unsatisfactory outcome in patients who fail to respond to conservative therapy within three months. They comment on the favorable prognosis of patients who show complete proctoscopic remission and point out that presence of ileal involvement of pseudo-polyposis does not affect the ultimate outcome. Bockus *et al.* (136) suggest the term "toxic aganglionic megacolon" when a fulminant course is associated with extreme colonic dilatation.

Complications.—Carcinoma continues to figure high on the list of preventable complications. Banks *et al.* (134) reported nine instances in 244 patients, seven of them with a duration of disease of more than 10 years, while Cullinan & MacDougall (135) found six carcinomata in 364 patients, four in patients who had had the disease longer than 10 years. Wilcox & Beattie (138) report the first authentic case of death in a child with carcinoma and chronic ulcerative colitis, while Thorlakson (139) gives an account of 12 cases of carcinoma in 182 colectomies for colitis. He believes that stricture development is often the earliest indication of malignant degeneration and he advises very close observation under such circumstances. Galambos *et al.* (140) report their experiences with exfoliative cytology in the diagnosis of malignant degeneration. Cells obtained by irrigation and suction of the rectum frequently gave false positive results, but cells obtained from higher in the bowel by colonic washing were more reliable. One certain and one possible (the patient died elsewhere) neoplasm were detected by use of this method. As it stands the technique is unreliable, but further developments should be interesting.

The conviction is growing that more elective surgery should be performed for the prevention of carcinoma (141, 142), a very reasonable one if, as appears likely, the mortality from surgery is less than the incidence of malignant degeneration in patients whose duration of disease is longer than 10 years.

Kelley & Logan (143) review the incidence of erythema nodosum in ulcerative colitis and feel that the figure of 2.5 per cent is probably an underestimate as they found six instances in a personal series of 71 cases. They emphasize that the appearance of erythema nodosum frequently indicates activity of the colitis. Finnerty (144) records six cases of ulcerative colitis whose presenting symptom was the result of an ano-rectal complica-

tion such as bleeding, fissure, or fistula. He stresses the hazards of surgical treatment in such patients.

Ulcerative colitis and pregnancy.—Banks *et al.* (134) have reported 87 pregnancies in 56 patients, MacDougall (145) 100 pregnancies in 64 patients, and Crohn *et al.* (146) 150 pregnancies in 110 patients. While all are agreed on the gravity of the prognosis and the severity of the condition when it makes its first appearance during pregnancy or the puerperium, differences of opinion are expressed of the effect of pregnancy on quiescent and active disease. Among patients with quiescent disease, Banks *et al.* found that pregnancy reactivated the condition in 18 per cent, and Crohn *et al.* in 54 per cent. None of MacDougall's patients were adversely affected. Pregnancy in patients with active disease was found by Banks *et al.* to cause improvement in 13 per cent, no change in 56.5 per cent, and deterioration in 30.5 per cent; by MacDougall, improvement in 60 per cent, no change in 25 per cent and deterioration in 25 per cent; and by Crohn *et al.*, deterioration in 73.6 per cent. The latter authors also noted that the effects were worse if the disease made its appearance during the first trimester and also that relapse or increase in severity were most likely to occur at this time. All agree that the abortion, stillbirth, and premature birth rates fall within normal limits. Crohn *et al.* point out that when pregnancy is associated with ulcerative colitis, normal delivery and a normal child usually result and, as a general rule, the mother's life is not threatened. On the other hand, the pregnancy may initiate a long period of ill health and termination may be considered if marked deterioration occurs or the disease makes it first appearance during the first trimester. These same authors have correlated, to some extent, the tendency for relapse on first appearance of the disease during the first trimester or the postpartum period with variations in blood estrogen levels.

The question of ileostomy and pregnancy was the subject of a study by Scudamore *et al.* (147) who reported a series of 18 pregnancies in 12 patients. They conclude that the ileac stoma had no adverse affect on the pregnancy and that normal delivery can be conducted. The pregnancy may cause minor ileostomy morbidity with local cracking, bleeding, prolapse, or obstruction, and it is advisable to defer pregnancy until at least a year after the ileostomy has been established. A noteworthy observation was that the abortion rate was significantly higher in these patients who still retained some diseased colon, a fact which was also emphasized by Swinton (148) in a discussion on ileostomy. It would appear wise to advise against pregnancy in such patients until all the diseased bowel has been removed.

Treatment.—No dramatic new treatments have been forthcoming. Monat (149) has reported spectacular results with the use of a gluten-free diet. Although his series was completely uncontrolled, the results are interesting. Steatorrhea is know to occur in a certain percentage of patients with ulcerative colitis (150) and possibly this aspect of treatment deserves further study. The accent continues to be on control of symptoms with careful nursing and control of nutrition and electrolyte balance. Of the anti-

biotics in current use, salicylazosulfapyridine (Azulfidine), has achieved great popularity (151, 152, 153), but the popularity is based on clinical impressions rather than on clinical trials. Numerous reports have appeared (154 to 158) testifying to the continued usefulness of steroids as an adjunct in the medical management of ulcerative colitis, but no further controlled trials have been reported. The general impression is that of all those available, ACTH is the most effective given as an aqueous intramuscular injection, followed by hydrocortisone, ACTH gel, prednisone, prednisolone, and cortisone in that order. Sklar *et al.* (159) have recently emphasized some of the hazards in the use of steroids in this condition, while Brooke (160) has suggested an additional danger in that continued administration of steroids may make the colon so friable as to make its handling almost impossible at subsequent operation. Truelove has reported his experiences (161, 162) with hydrocortisone applied locally by means of retention enemata, and considers the results sufficiently encouraging to warrant a clinical trial.

The importance of psychosomatic aspects and the value of psychotherapy have been re-emphasized by Groen & Van der Valk (163) and Paulley (164). A striking response to psychotherapy in a patient with fulminant disease is recorded by Bressler (165). Some indication of the limitations of this form of treatment can be gauged by the author's statement that "she was only seen for a relatively short time, i.e., fifty hours."

Progress continues in the surgical management of ulcerative colitis. Aylett (166) reports his further experience with total colectomy and ileo-rectal anastomosis. To date 47 consecutive cases have been so treated with two deaths (unrelated to the surgical procedure). Of these patients, 70 per cent have six or less bowel movements per day, 15 per cent have seven to ten, 4.5 per cent have more than ten, while 8 per cent have evidence of residual proctitis. At first sight the results appear impressive with a one to six-year follow-up, but the author does not consider the possibility of unconscious selection, neither does he specify the degree of rectal involvement present prior to operation. McCorkle (167) is similarly enthusiastic on the basis of four patients so treated, but Goligher (168) doubts the value of the procedure as five of his series of 15 patients subsequently needed ileostomy. Various authors testify to the value of a one-stage operation with proctocolectomy and ileostomy (169, 170, 171), and this would appear to be the operation of choice in patients subjected to elective surgery. Ileostomy problems have been considerably reduced since the development of the mucosal grafted ileostomy (172), while Swinton (148) and Brooke (173) have given a comprehensive review of present-day ileostomy problems. Brooke found that of 101 ileostomy patients, 92 were engaged in full-time work. Only five considered the ileostomy to be unsatisfactory, while a further 11 complained of occasional excoriation. Thirty-four suffered some discomfort on lifting or bending, while approximately half of the patients restricted their diet to some extent out of respect for the ileostomies. None of the men complained of impotence and two of the women had normal

pregnancies. The Rutzen bag has proved to be a great advance over previous appliances and the occasional development of allergy to rubber cement can be avoided by the use of a "Royal" appliance (171) which employs a pad of sponge rubber in place of cement. Swinton (148) comments on the value of the QT clubs, but his formidable list of postileostomy complications (obstruction 46.3 per cent, fistulae 22 per cent, skin irritation 15.9 per cent, electrolyte imbalance 12 per cent, herniation 4.2 per cent, stomal retraction 3.5 per cent, prolapse 0.3 per cent) emphasizes the fact that surgery is not yet the solution to the problem of ulcerative colitis.

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CARDIOVASCULAR DISEASES (MEDICAL)[1]

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ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

One of the most important developments in the field of atherosclerosis has been the publication of the report of the Cooperative Study of Lipoproteins and Atherosclerosis, a committee formed by the Advisory Heart Council of the National Heart Institute to examine the validity of biochemical methods for predicting clinical atherosclerosis (1). They found that elaborate methods for categorizing serum lipoprotein fractions in patients were no more reliable for this purpose than was a simple fasting blood cholesterol determination. Indeed, under certain conditions the simpler test proved to be a more sensitive index than such costly and widely publicized methods as the so-called "atherosclerotic index." However, Stare and his co-workers (2) point out that tests for identifying atherosclerosis can have only limited clinical usefulness no matter how accurate and sensitive they are, because (*a*) the disease is a chronic one and the critical lesion is unrelated to the rate of development of the chemical abnormality, and (*b*) thrombosis in a diseased, strategically located blood vessel more often precipitates the clinical disability than does the atherosclerosis itself.

Nevertheless, the results of the Cooperative Study support the theory that coronary artery disease is associated with a lipoprotein metabolic abnormality. Whether the association is a causal one is not yet proven but most workers tend to believe that it is, at least in part. There has been a great deal of interest in the demonstration that when more unsaturated fats are substituted in the diet, gram for gram, for highly saturated fats such as butter, there is a progressive fall of blood cholesterol levels (3, 4, 5). Preparations of unsaturated fatty acids are now commercially marketed for this purpose, to be used instead of butter and other animal fats in the diet. A number of other drugs and chemical agents such as desiccated thyroid, triiodoacetic acid, pyridoxine, β-sitosterol, and nicotinic acid are under intensive study for their cholesterol-lowering properties (6, 7, 8). Certain drugs once thought to be effective are now known to be relatively ineffective. This appears to be the case for inositol, methionine, choline, and lecithin (9). Estrogens also lower blood cholesterol levels, but their feminizing effect has prevented their wide use for this purpose. It is important to realize that while drugs and diets may lower blood cholesterol levels, it is not yet known that this will prevent human atherosclerosis, much less reverse established lesions.

For several years evidence has been accumulating indicating that the

[1] The survey of the literature pertaining to this review was concluded in September, 1957.

shock of acute myocardial infarction may not result from the loss of myocardial tissue but rather to a disturbance of a modulating feed-back nerve reflex between the left ventricle and the peripheral arterial system (10, 11). It is now generally accepted that there are such heart-peripheral arteriolar reflexes, and pressor receptor end-organ areas in the left ventricle have been identified in lower animals (12). Such a theory provides a rationale for the use of pressor amines in the treatment of the shock of myocardial infarction (13).

The problem of whether or not to give anticoagulants to patients with acute infarction is still unsettled. Both Wright (who feels that all patients with infarction should be so treated) and Russek (who feels that only the "poor risk" cases should be given anticoagulants) have continued to hold their ground (14, 15). Strong support for the Russek thesis comes from a careful and thorough study made by a group of British workers (16) who conclude, on the basis of a controlled series of 500 patients, that the anticoagulants had only slight beneficial effect on the mortality rate of the series as a whole, and this primarily in the more seriously sick patients. In any case, there appears to be agreement that the beneficial effects of anticoagulants are solely in preventing thrombo-embolic episodes; they do not significantly prevent extensions of the infarction or affect the rate of healing. Furthermore, anticoagulants, either heparin or bishydroxycoumarin (Dicumarol), will not usually prevent infarction when they are given during the premonitory phase (17, 18). Long-term treatment with bishydroxycoumarin following infarction has been reported by Keyes and his co-workers (19) to reduce materially the incidence of and mortality from later infarction. However, this use of anticoagulants will be even more difficult to evaluate than is the treatment of acute attacks, and longer follow-up periods will be needed to settle this important issue. Wright (20) has recently reviewed the comparative merits of various anticoagulating drugs.

Numerous studies attest to the value of transaminase determination in the recognition of acute myocardial infarction, especially if the level is over 100 units (21, 22). Walsh *et al.* (23) have found that pulmonary infarction and pneumonia can also produce levels as high, but the rise tends to be slower. Lieberman (24) points out that if a patient with a suspected infarction also sustains a cerebral vascular accident or injury to skeletal muscle the serum transaminase level is no longer a reliable indicator of infarction. Likewise, a tachycardia of over 160 produces a somewhat elevated level, as do acute rheumatic fever and other causes of myocarditis (25). Pericarditis does not elevate transaminase unless the epicardial layers of the myocardium are significantly involved. Most cases of coronary insufficiency and status anginosus have negative tests (26). A number of other myocardial enzymes have been studied for their usefulness in detecting infarction, and although some are technically simpler to perform than the transaminase test, none has proven to be significantly more discriminat-

ing of infarction (27, 28). Perhaps Genecin's (29) immunologic method for identifying enzymes of myocardial tissue from those of other organ tissues will lead to a test which is organ-specific. This would tremendously enhance the reliability and usefulness of the test.

HYPERTENSION

New drugs continue to be introduced for the treatment of hypertension. The most recent and promising is mecamylamine which is another ganglionic blocking agent. It has the important advantage over other blocking agents of its type in that it is completely absorbed on oral administration and therefore the oral dose of the drug is the same as its parenteral dose. The hypotensive effect is similar to that of pentolinium tartrate and hexamethonium bromide but it is longer acting, allowing easier control. Side effects, such as dryness of the mouth, constipation, urinary retention, nausea, and vomiting are more common than with the other blocking agents. Unlike hexamethonium and pentolinium, the patient does not develop "tolerance" to the drug (30, 31, 32).

A small percentage of patients receiving hexamethonium develop a reversible but occasionally severe pneumonitis which is similar to the pneumonitis seen in uremia and in acute rheumatic fever; it is apparently caused by exudation from the pulmonary capillaries into the alveoli (33). Hydralazine hydrochloride (Apresoline) in addition to producing a lupus-like syndrome (34), is reported to increase the incidence of angina pectoris in patients predisposed to such attacks (35). Abrahams (36) studied the effects of depressor drugs in patients with hypertension and renal failure and found there is no acceleration of renal deterioration with pentolinium or hydralazine but the renal lesion is usually not improved. The psychic depression that is commonly seen with Rauwolfia administration is reported, in a study from the Mayo Clinic (37), to result not from a chemical effect of the drug but as a personality reaction to the release from inhibitions experienced during the first stages of therapy.

A newly discovered cause of hypertension is the excessive secretion of aldosterone by the adrenal cortex; usually a tumor of the adrenal cortex is responsible (38, 39). One should always consider the possibility of hyperaldosteronism when a patient with hypertension complains of inordinate thirst and polyuria, because aldosterone plays an important physiological role in the regulation of body fluids and electrolytes. The diagnosis is strengthened by finding excessive potassium in the urine and is proven by the presence of excessive aldosterone in the urine. The hypertension may sometimes be very severe and mimic hypertension of any other cause (40). Surgical removal of the tumor cures the hypertension.

Another type of surgically curable hypertension is that caused by unilateral renal disease. Twenty-one patients proven to have this disorder have been studied at the Johns Hopkins Hospital (41). The most reliable method for making the diagnosis was the demonstration of a lower sodium concen-

tration and lower urine flow in the diseased kidney than in the normal kidney on ureteral catheter study. Pathologic examination of the kidney in these patients showed ischemic tubular necrosis similar to that seen in the Goldblatt kidney. A useful clinical clue to this disorder, pointed out by Merrill and his colleagues (42), is the syndrome of leukocytosis, polyuria, and albuminuria with diminished ability to concentrate urine. Another clue is the finding of an abnormally small kidney shadow unilaterally on abdominal x-ray. Usually this type of hypertension advances rapidly with prompt appearance of severe headaches and retinopathy. Mild hypertension appears to be rarely the result of unilateral renal disease. Occasionally the unilateral renal disease is attributed to an extrarenal process, for example, an everted atherosclerotic plaque in a renal artery (43) or an embolic renal infarction (44) rather than to parenchymal disease of the kidney.

In evaluating the effectiveness of any measure for the treatment of hypertension, the role of psychologic factors must be considered. Schroeder & Menhard (45) found that when the blood pressure is measured every few hours for three days, many patients believed to have severe hypertension on the basis of their initial blood pressure determination prove to have normal blood pressure. Goldring and his co-workers (46) and Shapiro (47) have examined the role of suggestion in the successful treatment of hypertension and have produced "cures" as far as the blood pressure is concerned, by the administration of drugs known to be without cardiovascular effects. Most workers in this field are of the opinion that only when the hypertension causes objectively demonstrable damage to one or another organ system is vigorous treatment with the more potent depressor agents warranted.

ELECTROCARDIOGRAPHY

Present day views on the nature of membrane potentials and the properties of the body as a volume conductor, the two fundamental premises on which all electrocardiographic theory rests, were the subject of a symposium sponsored and later published by the New York Academy of Sciences (48). As presently understood, the membrane events can be summarized as follows: with arrival of excitation at the myocardial cell membrane, there is a change in permeability to Na^+ and K^+; Na^+ enters the cell producing a reversal of transmembrane potential which accounts for the rise of the R wave of the cellular QRS complex; then K^+ escapes from the cell abolishing the potential and returning the R wave to zero; a slow return of K^+ into the cell and Na^+ to the surface accounts in general for the cellular T wave. The mechanism responsible for the change in cellular permeability and the role of cellular "pumps" in the ion migrations have been studied by several workers (49, 50), and the subject has been reviewed by Nachmansohn (51).

Regarding the volume conductor properties of the body, there was

agreement among the participants at the symposium that, in general, body surface leads in man record the electrical events of the heart as if they were all generated from a single point-source within the heart. Thus, most, if not all, body surface leads must be recording from essentially the same P, QRS, and T electrical forces. This is a considerably different way of looking at the electrical field of the heart than has prevailed in the past, and it can safely be said that there is no longer any substantial experimental or theoretical support for the "unipolar" theory of clinical electrocardiography, in which each body surface lead is considered to be primarily a record of the electrical events emanating from the region of the heart facing the electrode. This change in point of view has led to a re-examination of the adequacy of the lead system used in conventional clinical electrocardiography. It has been shown quite clearly that the Einthoven limb leads are asymmetric with regard to the electrical field of the heart, and the use of an equilateral triangle or triaxial reference figure for their analysis contains some error (52, 53). As a result of such studies, a number of new lead systems have been recommended which are believed to be more accurate and certainly are more rational than the twelve lead system generally used in clinical work (54, 55, 56). However, the new systems require different electrode locations and involve additional and often costly circuitry. The amount of error in the conventional twelve lead system is not known with certainty; it doubtless varies from patient to patient and it may not be great for clinical diagnostic purposes. For example, most clinical ECG diagnoses depend upon deflection components of at least .03 sec. duration and on deviations of manifest electrical forces of at least 45° from the normal direction (57). With such a wide tolerance in phase, duration, and direction of electrical forces in clinical diagnosis, the new lead systems may not greatly improve the sensitiveness of electrocardiography for clinical diagnosis until more progress is made in clinical interpretation itself. For the same reason high fidelity or ultra high frequency electrocardiography has not yet proved to be useful in clinical diagnosis (58, 59). Schaffer has recently written a nontechnical review of the newer concepts in the volume conductor problem and the search for new lead systems (60)

The cathode tube method of vectorcardiography continues to engage the attention of many workers. So far, this technique has been used principally for collecting "patterns" of loops in various planes of the body for a number of different electrocardiographic syndromes (61, 62). In the majority of cases, the data contained in the loops can be readily identified in the conventional clinical tracing for, in general, the two methods are recording from essentially the same electrical forces. It is frequently claimed that the cathode tube method of recording cardiac electrical activity is superior for clinical purposes to the conventional tracing. However, no cases have so far been published which, in the opinion of the reviewers, prove this when vector methods are used to study the conventional tracing;

and there are certain QRS and T diagnoses which the cathode tube vectorcardiogram will miss but which are readily seen in the conventional clinical tracing (63, 64).

A different use of the cathode tube technique has been made in isolating electronically certain parts or properties of the cardiac electrical forces which can be seen only with difficulty or not at all in the conventional tracing. Such properties as the lie of the plane of the QRS loop (65), the rate of growth and rate of rotation of the cardiac vector during a single QRS interval (66, 67), and amplified components of the QRS or other forces (68) are being studied. These analyses may prove to be of considerable clinical value, especially in instructing the clinician to see data in the conventionally recorded deflections which he has not previously recognized.

Several workers have been studying the way in which activation spreads through the wall of the heart, using modern electronic recording methods with multiple microelectrodes inserted into the ventricular wall. The studies are of considerable theoretical interest but, as the investigators point out, there is a major difficulty in applying their findings to clinical electrocardiography: the deflection in the clinical tracing is a summed record of electrical activity from all regions of the heart, and it is not known to what extent the potential recorded at a point within the myocardium is participating, if at all, in writing the deflection in a body surface lead (71, 72). As far as QRS forces are concerned, Prinzmetal (69) and Durrer (70) found no resultant QRS voltage from the inner third of the left ventricular wall and concluded that this region is electrically "silent." They explain their observation by suggesting that excitation is initiated in these layers by tiny islets of depolarization which have no resultant voltage until they coalesce and reach the endocardial surface. However, Scher (73) and Cortes (74) have not been able to confirm this concept of a "silent" endocardium, using what appear to be better recording techniques.

The intramural microelectrode method has also been used to study ventricular conduction defects (75). However, here also the experimental findings may have only a limited application to the clinical problem because experimental bundle branch block is different in certain regards from bundle branch block in man. For example, in right bundle branch block in man there is no change in the first 0.04 sec. of the QRS complex in the various leads, while in experimental right bundle branch block the entire QRS complex is altered (76). The lesion responsible for right bundle branch block in man must lie much farther out in the wall of the right ventricle than it does in experimental block. And Braunwald (77) has shown that in certain patients with tracings fulfilling the criteria for the diagnosis of left bundle branch block, left ventricular systole is not delayed after right ventricular systole. It is surmised that in these cases the conduction defect lies distal to the left main bundle and is perhaps sometimes a diffuse lesion in the free wall of the left ventricle.

In contrast with previous views, it has been shown that ventricular conduction defects are not always associated with prolongation of the QRS interval (78, 79, 80). Examples of this have been seen in man during tachycardia (81), nodal escapes (82), quinidine administration (83), and hypokalemia (84). The syndrome of peri-infarction block is another example of a ventricular conduction defect which may have little or no QRS interval prolongation (57), and there is both experimental and clinical evidence to indicate that most cases of marked left axis deviation arise from a conduction defect in the free wall of the left ventricle even when there is no QRS prolongation (80, 85).

The use of the electrocardiogram in the diagnosis of congenital heart disease has received considerable attention in recent years. Cabrera (86) introduced an electrocardiographic method for differentiating ventricular enlargement caused by increased flow as in intracardiac shunts (the "diastolic overload pattern"), from that stemming from increased resistance as in congenital valvular stenosis (the "systolic overload pattern"). Although from his own data there is only limited statistical validity for some of the patterns he has emphasized for the two syndromes, the method has drawn attention to the fact that increased flow in a chamber may produce the electrocardiographic effects of ventricular enlargement. For example, a prominent R′ in the QRS complex at V-1 is a part of the "right ventricular diastolic overload pattern." This pattern is seen in the majority of cases with increased right ventricular flow due to an atrial septal defect of the secundum type or to anomalous pulmonary venous return. However, there are other right ventricular and left ventricular causes of an R′ at V-1 (85) and the mechanism responsible for the deflection in interatrial septal defect is still debated (87, 88). Quite clearly it is attributable neither to the increased flow itself nor to hypertrophy, for after the atrial septal defect is closed surgically the basic R′ pattern usually persists; perhaps in these cases it comes from a right ventricular conduction defect resulting from the marked right ventricular dilatation produced by the shunt.

The electrocardiographic abnormality in the persistent ostium primum type of atrial septal defect is quite different from that found in the ostium secundum type (88, 89). In persistent ostium primum there is marked left axis deviation of the initial half of the QRS complex on the various leads, with evidence of a right ventricular conduction defect in the terminal part of the QRS complex. A high percentage of cases of atrioventricularis communis also show this type of electrocardiogram (90). Formerly, tricuspid atresia was thought to be the only cyanotic congenital heart disease which might have left axis deviation; its left axis deviation differs from that of persistent ostium primum in that there is usually no right ventricular conduction defect in addition to the left axis deviation (91). Single ventricle, fibroelastosis, and truncus arteriosus may occasionally also show marked left axis deviation with or without the conduction defect (92, 93).

ARRHYTHMIAS

The controversy over the mechanism of atrial fibrillation, whether caused by an ectopic firing focus or by a circus mechanism in the atrium, still engages the attention of investigators. Prinzmetal, who is one of the principal exponents of the former view, has extended his studies to man using cinematographic and direct epicardial lead techniques to support his thesis (94). The studies clearly demonstrate the fractionation of atrial activity in this arrhythmia but shed light only indirectly on the actual firing mechanism. While clinicians tend to accept Prinzmetal's view, physiologists consider the point unsettled. For example, Lanari and his co-workers (95) have shown that either mechanism can take place, and indeed have produced both mechanisms in the same animal at once. They report that topical application of aconitine (which is the method used by Prinzmetal in most of his experiments for producing atrial fibrillation) usually acts by setting up a rapid ectopic firing mechanism, while electrical stimulation (which is the method used by Sir Thomas Lewis, the originator of the circus mechanism theory), usually produces atrial fibrillation by a circus mechanism. Which of the two mechanisms most closely resembles the mechanism in man is not known. But the firing mechanism is only a portion of the mechanism of atrial fibrillation. Were it not for the interlacing syncytium of the atrial musculature, fibrillation could not take place no matter what the firing mechanism. Brooks and his co-workers (96) appear to be the only workers who have taken this factor into consideration in explaining atrial fibrillation.

Burn and his colleagues (97) have shown that acetylcholine enhances the experimental production of atrial fibrillation, presumably by accelerating return of K^+ into the cell thereby shortening the refractory period. Perhaps this explains the occasional production of atrial fibrillation (98) and conversion of atrial flutter to atrial fibrillation (99) by carotid sinus pressure. There is evidence that potassium influences the ventricular rate in atrial fibrillation, for when potassium depletion takes place as a result of diuresis in patients with atrial fibrillation and congestive heart failure, the ventricular rate has been reported to rise as high as 160 per min., with prompt return toward normal when potassium was restored (100). Dietz and his colleagues (101) have demonstrated that one atrium may fibrillate while the other is in normal sinus rhythm, a phenomenon which has been seen from time to time in the experimental animal but infrequently demonstrated in man. Daley & McMillan (102) have shown that during atrial fibrillation the normal mitral valve becomes incompetent and, in the presence of mitral stenosis, a higher than normal mean atrial pressure is necessary for ventricular filling. This may explain why patients with mitral stenosis often have greater disability when they are fibrillating, even when the mean ventricular rate is relatively normal.

Lown & Levine (103) have shown that the potassium depletion which follows a mercurial diuresis is an important cause of paroxysmal atrial

tachycardia with block in patients receiving digitalis. Potassium administration promptly terminated the arrhythmia. They suggest that the low serum potassium enhances the toxic and arrhythmic effects of digitalis.

Brodie and co-workers (104) have recently reviewed the pharmacology and clinical effectiveness of procaine amide in the treatment of arrhythmias. Most workers feel that procaine amide and quinidine are of nearly equal effectiveness in the treatment of ventricular arrhythmias, but that quinidine is more effective than procaine amide in the conversion of atrial fibrillation to a normal sinus mechanism. The incidence of serious or alarming toxic effects is apparently somewhat greater with quinidine administration while minor toxic effects and patient-dislike are more commonly seen with procaine amide. The sudden death which takes place in rare cases of atrial fibrillation shortly after conversion by quinidine has in the past been attributed to cerebral embolism, the embolus presumably breaking loose from a left atrial thrombus when effective atrial contractions begin. However, it has been pointed out that were this the case the incidence of nonfatal arterial embolism should be higher following conversion than it is in most series of cases (105, 106). It has been shown both experimentally and clinically that quinidine itself can produce ventricular arrhythmias, and it is now believed that at least certain of these fatalities are due to ventricular standstill or ventricular fibrillation produced by the quinidine (107, 108, 109). If this is true, the use of procaine amide may prove to be no safer in this regard, because Grumbach (110) has shown in animal experiments that it [and potassium and most other agents which are used for their irritability depressing properties (111)] will also produce ventricular arrhythmias under certain circumstances. Even molar lactate, which Bellet (112) has frequently recommended for the treatment of complete heart block and other arrhythmias, occasionally produces ventricular tachycardia (113). Perhaps Grumbach's observation that epinephrine terminates the ventricular arrhythmia produced by procaine amide will prove to be an important lead in the clinical treatment of these complications. In this connection, Brofman and co-workers (114) have found that an interface in the myocardium between normal and anoxic tissue becomes a site of increased irritability, and they believe this is responsible for the ventricular arrhythmias of acute myocardial infarction. If this is true it may sometimes be more important to restore adequate coronary flow by the use of pressor agents than to depress the irritable focus by the use of procaine amide or quinidine in patients with ventricular fibrillation.

VALVULAR DISEASE

An important new insight into the mechanism of rheumatic valvular deformity is reported by Tweedy (115) who showed that the valvular thickening and chorda fusion result from a transformation of deposited fibrin rather than from fibroplasia with "fibrinoid degeneration," a term which he feels should be discarded. A similar mechanism is perhaps the

basis of fibroelastosis of the endocardium (116), the pulmonary vascular lesion of recurrent pulmonary embolism (117), certain types of myocardial lesions (118), and perhaps even certain aspects of atherosclerosis (119). Perhaps several of the illnesses now considered "collagen" or "connective tissue" diseases will prove instead to be caused by abnormalities of fibrin deposition.

Hecht and his co-workers (120) and MacKinnon and his colleagues (121) point out that in the presence of markedly elevated pulmonary artery pressure in patients with severe mitral stenosis the mitral diastolic murmur may be inaudible, and catheterization of the left heart may be necessary to prove the diagnosis. Edwards *et al.* (122) and Davis & Andrus (123) have described congenital and acquired lesions of the left atrium and mitral leaflets which may simulate rheumatic mitral valve disease.

It has often been noted that the subjective benefits of mitral commissurotomy for mitral stenosis are not paralleled by improvement in catheter findings. Donald, Bishop & Wade in England (124) have completed an important, detailed follow-up study of the hemodynamics in 27 patients four to seven years after commissurotomy. All patients had been greatly if not totally relieved by the surgery, yet all of them continued to show rises of pulmonary artery pressure on exercise to levels nearly as high as those recorded preoperatively; on the other hand, the ventilatory cost of exertion was less after successful surgery. In other words, the heart behaved on exercise essentially as it did prior to the surgery but the hemodynamic alteration no longer led to dyspnea. It has long been known that the patient with mitral stenosis ventilates more than the energy cost of exercise would seem to warrant, and surgery apparently reduces this (124, 125). Only in part is the improvement traceable to a reduced volume of blood in the lungs, with less "stiffness" of the lung on breathing (126, 127). Clearly, more studies of this type will be necessary before the salutary effects of mitral commissurotomy will be completely understood.

Larson (128) has reviewed the postcommissurotomy syndrome, a febrile, pleuritic, pericarditic illness which develops weeks or even months after commissurotomy. Study of the syndrome is still hampered by lack of any specific laboratory or clinical test which positively identifies it, and many workers are of the opinion that several different disorders may be responsible for the illness. There has been no serologic confirmation of the view formerly held that it is due to recrudescence of active rheumatic fever (129), and several cases indistinguishable from it have been described following surgery for nonrheumatic conditions, including cases where the pericardial sac was not entered (128). Dressler (130) and Stein (131) have called attention to a similar syndrome which may develop following acute myocardial infarction. Penicillin does not reduce the incidence of the postcommissurotomy syndrome (128); however, Dresdale (132) has evidence that steroid administration may.

Bauer and his co-workers (133) and Schilder *et al.* (134) have further

defined the aortic insufficiency seen in rare cases of rheumatoid spondylitis. It occurs almost exclusively in males; the aortic valvular lesion is quite different from that produced by rheumatic fever—indeed, it more nearly resembles the valve lesion of luetic aortitis, except that the aorta itself is not involved. In a hemodynamic study of aortic stenosis, Gorlin (135) found that the hydraulic effect of the obstruction of aortic stenosis is often extraordinarily severe before clinical evidence of heart failure appears, with a pressure drop across the aortic valve of 150 to 200 mm. Hg. On exercise the flow across the stenotic aortic valve is usually not increased in spite of the increased heart work; perhaps this partly explains the exertional syncope and angina which these patients suffer. When heart failure develops in such patients the flow across the valve diminishes and, as a result, there is a marked dimunition in the intensity of the aortic systolic murmur. The prognosis of rheumatic aortic insufficiency has been studied by Bland (136) from the 20-year follow-up study of patients at the Good Samaritan Hospital in Boston. One third of the 87 patients are still fully active 20 years following the initial discovery of their lesion. The development of angina pectoris proved to be an ominous finding in these cases of rheumatic aortic insufficiency.

PULMONARY VASCULAR DISEASE

The pulmonary hypertension which frequently complicates both congenital and acquired heart disease continues to be an important clinical problem for it accelerates cardiac failure and often contraindicates surgery for otherwise correctable cardiac defects. In a study of the pulmonary vascular pathology in congenital heart disease with increased pulmonary flow, Heath & Whitaker (137) found that pulmonary vascular histology was normal when there was no increase in pulmonary artery pressure, but changes were observed when the pressure was elevated. Edwards, in a recent review of the problem (138), points out that the fetal lung normally provides a high resistance to flow which is associated with a type of arterial hypertrophy not seen in the adult lung. He suggests that the abnormal pulmonary vascular histology found later in life in certain congenital heart conditions with increased flow may develop from persistence of this fetal vasculature. He has also shown that the pulmonary arterial tree of the fetal lung has a considerable component of reversible vasoconstriction, the persistence of which may play a part in the pulmonary hypertension of congenital heart disease. When the increased flow persists long after birth further pathologic changes develop, leading to a relatively irreversible degree of pulmonary hypertension. Dammann & Ferencz (139) have found that when the pulmonary vascular changes include medial hypertrophy and intimal sclerosis, the irreversible stage may have been reached, in which case surgery is hazardous. Adams (140) has put this observation to practical use and finds that preoperative biopsy study of the pulmonary vessels is useful in deciding whether or not the risk of corrective surgery is justified

in cases where increased pulmonary vascular resistance is already established. Studies of the changes in the pulmonary vascular pathology following successful surgery are not numerous, but Heath & Whitaker (141) report that the vascular lesions seldom regress although damaging pressures may fall. In studies of the effects of experimental pulmonary hypertension on the vascular tree of the dog's lung, Ferguson *et al.* (142) have found that even severe changes were slowly reversible if the pulmonary hypertension was not of long duration.

It has been the hope of workers in the field that the pulmonary arterial hypertension of congenital and acquired heart disease might respond to pharmacological vasoactive agents. This hope is based in part upon the early observation that hypoxia produces a reversible although slight pulmonary hypertension, a subject which was reviewed recently by Cournand in his Nobel Award Dissertation (143). Many of the observations made on vasomotor effects in the pulmonary circulation have been based on unusual conditions, and the extent to which these effects might be playing a part in man is still unclear. Several investigators (144 to 147) have recently studied the effects of various agents on the pulmonary hypertension of congenital heart disease, mitral stenosis, and primary pulmonary hypertension, but, so far, they have been able to alter pulmonary vascular resistance only slightly, briefly, or with accompanying systemic hypotension of a disabling degree. Dresdale reported that tolazoline hydrochloride (Priscoline) was effective for this purpose, but most subsequent studies have found its effect disappointingly slight. The same, by and large, is true of other agents such as hexamethonium, acetylcholine, and dihydroergotamine.

Several cases of the still mystifying idiopathic or "primary" pulmonary hypertension have been reported (148, 149, 150). It occurs nearly exclusively in women, but the possibility that the pulmonary vascular lesion results from recurrent postpartal embolism is unlikely in view of the fact that four of Shepherd's nine female patients had never been pregnant. The disease usually runs a rapid course once symptoms develop, but Chapman reports one patient who is still leading a reasonably comfortable life 12 years after onset of exertional dyspnea.

An interesting cardiopulmonary syndrome associated with marked obesity has been reported by Sieker and his associates (151). It is characterized by somnolence, periodic respiration, cyanosis, polycythemia, and a rightward electrical axis. Frank right-sided failure is frequently present. It is believed to be caused by hypoxia as a result of the impaired bellows-action of the chest. Weight loss has been accompanied by uniform improvement according to this and other reports (152, 153).

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DISEASES OF THE AORTA[1]

By S. H. Boyer, IV, M.D., and V. A. McKusick, M.D.

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Aneurysm: General Considerations

Fundamentals in aneurysm formation were discussed by De Takats & Pirani (48) and by Blakemore & Voorhees (20). Abdominal localization of atherosclerotic aneurysm may be related to the higher peak systolic pressure, wide pulse pressure, and sharper pulse rise in this part. The predominant localization of syphilitic aneurysm in the ascending aorta (also cystic medial necrosis and the change of the Marfan syndrome) may be related to the fact that expansile pulsation is maximal there. A vicious cycle in aneursym formation is evident from the considerations of Laplace's Law: as the radius increases, wall tension increases, and so on. That special variety of aneurysm, poststenotic dilatation, was investigated in models by Holman (91). He concluded that distal to an obstruction, structural fatigue results from pounding of eddy currents produced by impact of a jet of high velocity on the slow moving fluid downstream.

Atherosclerotic and Syphilitic Aneurysm

Incidence and location.—Necropsy studies showed that syphilitic aneurysms were confined to the thoracic aorta in 89 (197), and 100 (38) per cent of cases. Sixty-three to 93 per cent of atherosclerotic aneurysms occurred in the abdominal aorta. Many (20, 24, 145, 197) note the marked decline in incidence of all syphilitic aneurysms. Atherosclerotic aneurysm may be increasing (125), possibly at a faster rate than the mean age of the population.

Prognosis.—Results of various analyses of prognosis of aneurysm are remarkably divergent (20, 24, 38, 44, 64, 80, 104, 158, 195, 197), largely because different types of cases, ascertained by different methods, have been used. Clearly the risk of rupture of arteriosclerotic aneurysm is considerable, although other complications of generalized arteriosclerosis are frequently the cause of death.

Symptoms and signs.—In abdominal aneurysm tenderness on palpation is often a conspicuous feature; pulsating abdominal mass may not be demonstrable and, in some, spontaneous pain is absent (63). Change in belt size may be the only symptom (57).

The abdominal aorta in elongating tends to bow to the left. Abdominal aneurysms are likely to present on the left side. Since the bifurcation of the aorta is about at the level of the umbilicus and most atherosclerotic aneu-

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rysms arise between the renal arteries and the bifurcation, they are likely to be palpable in the epigastrium, especially on the left. Rupture into the duodenum (94) is another indication of their high location. Indeed, Abramson & Jameson (2) describe a case of iliac artery aneurysm which ruptured into the duodenum.

Rupture of an abdominal aneurysm is likely to be announced by severe continuous pain (98), enlarging abdominal mass especially on the left, and signs of blood loss. Renal colic may be simulated (63) and if the hematoma presents in the inguinal area, after dissecting retroperitoneally, strangulated hernia (17) may be simulated. Several days to a week may elapse between onset of rupture and death (98, 196).

Franklin & Pollock (67) reviewed 128 reported cases of rupture of thoracic aneurysm into the superior vena cava. Eiseman & Hughes (61) repaired an atherosclerotic abdominal aneurysm which had ruptured into the inferior vena cava. Not only may thoracic aneurysms rupture into the pulmonary artery (31, 53) but also they may compress the pulmonary artery producing proximal pulmonary hypertension.

Roentgenographic signs, especially calcification in the aneurysm, allow detection of asymptomatic patients (63). Aortography has been reviewed (39, 76, 132) and it is concluded (39, 132) that abdominal aortography should be reserved for patients in whom the diagnosis is in doubt. This conclusion was based, in one instance (132), on a questionnaire survey of over 13,000 cases. Most surgeons consider aortograms not to be essential to the planning and execution of operation for abdominal aneurysm.

Steinberg & Finby (180b) believe that angiocardiography is satisfactory for the diagnosis of most lesions of the thoracic aorta and that the hazards of aortography can be avoided. For delineation of thoracic aneurysms Levene *et al.* (114) favor fluoroscopy and films in the right posterior oblique position.

Surgical treatment.—The most spectacular recent development in connection with aortic disease is the surgical resection of aneurysms with graft reconstruction of the aorta (122). Procedures designed to promote intraluminal thrombosis or mural fibrosis have been demonstrated to be of doubtful efficacy as the only treatment (19, 46, 156), and are now largely abandoned. Wright *et al.* (196) and most others believe that surgery of abdominal aneurysm is indicated even in asymptomatic patients if the general condition is good enough to tolerate surgery. Some (8, 156) counsel caution in patients over 70 years of age. Grafts of synthetic material seem to be as satisfactory as homografts (49). However, the long-term results remain to be described in detail. There was a failure rate of about 7 per cent in one short term clinical study (41b).

Death rates attributable to operation for abdominal aneurysm have been reported as 0 (191), 12 (9), and 13 per cent (156). In the largest series, 203 cases of DeBakey, Cooley & Creech (44), operative mortality was 8 per cent; of the last 56 patients, only one died. Twenty per cent were older

than 70 years. Operative mortality was greater in patients older than 70, with blood pressure over 150/90 mm. Hg or with associated heart disease. Survival in each of the first three years after operation was 82, 72, and 69 per cent. With operative intervention, survival of cases of ruptured abdominal aneurysm has been reported in 1 of 7 (9), 2 of 4 (98), 3 of 6 (168), 4 of 7 (189), and 18 of 27 (44).

In the small proportion of cases in which the renal arteries are involved, surgery, although more difficult, has been successfully performed (47, 62) by use of hypothermia or temporary shunt or both.

Excision of saccular thoracic aneurysms with lateral suture of the aorta has been successful in the hands of several surgeons (10, 44, 103). Total aortic arch resection with graft replacement is likely to be possible (41a, 123).

Traumatic Aortic Rupture and Aneurysms

Automobile accidents are the most common cause of traumatic rupture (77, 99, 146, 198). The isthmus, specifically the posterior convexity of the first part of the descending aorta, is the single most frequently involved site—over ⅓ of cases (146). In about ⅓ of cases there is minimal or absent external evidence of chest injury. For the false aneurysms which are particularly likely to develop just beyond the mouth of the left subclavian, resection is the treatment of choice (77, 181).

Rupture limits for the aorta are about 580 to 2500 mm. Hg (199). For this reason, Zehnder (199) maintains that chest compression, resulting in a tensile stress on the overstretched convexity of the aortic wall surrounding an incompressible fluid, is necessary for rupture to occur. He offers a vivid analogy to the effect of bending on a tensely distended and arched length of garden hose. Relatively firm fixation of the aorta at the isthmus and freedom of the descending aorta to be displaced forward during horizontal acceleration increase the bend on the posterior convexity of the isthmus region (99).

Lichtblau & Wilson (115) described fatal rupture of the aorta during surgery to correct spinal deformity of Marie-Strumpell spondylitis. Fibrous fixation of the aorta to the spine as a result of extensive x-ray therapy may be a factor. Fatal perforation of the esophagus and aorta by a piece of wire is described by Birrell & Syme (18). Aneurysm of the aortic arch may occur as a complication of fracture of the first rib (92).

Aortic Sinus Aneurysms

In the last few years the reported cases of sinus aneurysm rupturing into the heart, usually the right atrium or ventricle, have multiplied rapidly (7, 11, 25, 26, 59, 65, 75, 95, 116, 138, 143, 163, 189). Unruptured sinus aneurysms are discussed by Steinberg & Finby (180a). The association with coarctation (56, 74), pseudocoarctation, and the Marfan syndrome is noteworthy. Syphilis is sometimes the cause.

The right coronary sinus is most commonly involved by congenital aneurysm (163). Edwards & Burchell (60) conclude that the essential defect is a lack of normal continuity between the elastic lamellae of the aortic media and the cardiac annulus fibrosus.

Oxygen step-up on right heart catheterization is very helpful in the diagnosis. Retrograde aortography through a catheter introduced into the aorta is also helpful (25, 116); regurgitation of dye into the right side is facilitated by temporary occlusion of venous return to the heart (25).

Successful closure of ruptured aneurysms has necessitated use of hypothermia or pump-oxygenator for cardiac by-pass or both (7, 75). At the National Heart Institute a prothesis resembling a golf tee was devised (11) and used with success in a patient.

Uncommon Causes of Aortitis and Aneurysm

Mycotic aneurysms of the aorta have recently been reviewed and 12 new cases described (145). Aortic tuberculosis, developing from embolism to the vasa vasorum or by direct extension from neighboring lesions (190), may lead to direct perforation or to false aneurysm. Tuberculous aneurysm of an aortic sinus with rupture may complicate tuberculous pericarditis (66). Abdominal aneurysm associated with lymphadenitis has been successfully repaired (157). Rupture of the aorta is a rare complication of tuberculosis of the spine (175).

Reid (154) points out that every adequately studied case of temporal arteritis has had changes in the aorta. Dilatation of the ascending aorta (69, 154), stenosis of the branches of the arch (161), and even dissecting aneurysm (110) may occur.

Aortitis limited to the first few centimeters of the ascending aorta may occur in association with rheumatoid arthritis and especially rheumatoid spondylitis (34, 165).

Mammoth poststenotic dilatation of the ascending aorta may occur with aortic stenosis (51). Dissecting aneurysm may complicate the process (135, 149).

Aortic Dissection (29)

(Dissecting Aneurysm, Medial Hematoma, Dissecting Hematoma)

Etiology and pathogenesis.—Since the original description by orthopedists (150) there has been adequate confirmation (112) of the occurrence of saccular and dissecting aortic aneurysm in weanling rats fed the seeds of the ordinary garden sweet pea (*Lathyrus odoratus*). The toxic principle has been shown to be beta amino-propionitrile (166). The association with skeletal lesions led to analogies to the gene-determined defect of the Marfan syndrome (13, 133). There is also a possibility that aortic dissection is an integral part of the Ehlers-Danlos syndrome (133).

Metabolic factors in aortic dissection in man are further suggested by (*a*) the possible relationship of forced feeding to an epidemic of aortic

dissection in turkeys (136); (*b*) the aortic medial necrosis in vitamin E-deficient animals (119); and (*c*) the occurrence of dissection wtih hypothyroidism (54, 109). Beaven & Murphy (14) reported dissection in 9 of 44 patients with severe hypertension treated with methonium. The mechanism is not understood completely although wide fluctuations in blood pressure may be a factor. About 50 per cent of women who suffer dissection under 40 years of age are pregnant or recently pregnant (124, 167). Rupture is most frequent in the third trimester at the time circulatory volume and cardiac output reach a peak (147). The role of the effects of hormones on connective tissue remains speculative.

Cystic medial necrosis, the usual histologic substrate of dissection, is conceived (29, 135) to be a nonspecific morphologic expression of stress on the aorta—either physiologic stress on a genetically defective aorta or unusual stress on a "normal" aorta. In addition to dissection, idiopathic medionecrosis may lead to detachment of an aortic cusp (89, 130) and to aneurysm of the ascending aorta (10, 131). Longitudinal cleavage of the aortic wall without rupture and without intramural hemorrhage is described (12).

Atherosclerosis is not a factor of primary importance in dissecting aneurysm. Cases of ruptured atherosclerotic abdominal aneurysm have been labelled, probably improperly, dissecting aneurysm because short splits were found (101).

Clinical appearance.—General descriptions have been given (6, 29, 68). Although not the rule, prolonged hypotension may occur (200). The mimicry of myocardial infarction (27), recurrent tuberculous or idiopathic pericarditis (78, 134), cerebrovascular accident (72), acute surgical emergency of the abdomen (152), and other conditions is evident from recent reports.

Clinical oddities include ecchymoses over the upper chest and neck (183), hemoptyses (68), hyperbilirubinemia (68), and a newly developed musical murmur over the ascending aorta (134). The last may represent vibration of the intimal lip, fibrous cords, or other anomalous structure resulting from the dissection.

Surgical therapy.—Since, in most patients who survive dissecting aneurysm "re-entry" is found (174), Gurin (85) in 1935 and Shaw (173) in 1955 attempted creation of re-entry surgically. Selection of cases is difficult. Benson *et al.* (15) suggest that evacuation of clot in the process of the "re-entry" or "fenestration" operation may actually favor external rupture. Operative mortality is high. However, there are isolated reports of apparent success (73, 182). DeBakey, Cooley & Creech (44) operated on 16 patients, with success in 13, who remained asymptomatic for periods as long as 2 years.

Occlusive Disease of the Aorta

The aortic arch syndromes.—[Syn.: pulseless disease, Takayashu's (or

Takayasu's) syndrome, reverse coarctation, chronic subclavian-carotid obstruction syndrome (30), thrombotic occlusion of the branches of the aortic arch (43), Martorell's syndrome (43, 129)]. These disorders have as their common denominator the loss of pulses in one or more of the great vessels arising from the aortic arch (5, 23a, 71, 87, 161). Syphilitic aortitis has, in the past at least, been the most frequent cause. Aneurysm is by no means a necessary feature for development of obliterated pulses; pulse changes with syphilitic aortic aneurysm are infrequent. Intimal atherosclerosis, to which the syphilitic process in the media predisposes, is important in the luminal obliteration. Atherosclerosis alone is rarely the cause of full-blown changes. Stenosis of the left subclavian ostium is particularly frequent with atherosclerosis but rarely is the obliteration complete.

Total obliteration of the innominate, carotid, and subclavian ostia may be produced by syphilis or by the ill-understood entity referred to as "young female arteritis" (100, 107, 185). This disease, occurring particularly in women about 20 years old, has been described frequently in Japan and Scandinavia and increasingly in this country. Histologically, a granulomatous process with giant cells has been found in cases in which the changes have not advanced to nonspecific scarring at the time of examination.

Trauma, particularly blunt forms of injury to the upper chest as in steering wheel accidents, may play a role in the subsequent development of ostial obliteration. Injury to elastic lamellae probably predisposes to intimal atherosclerosis at a later date. Mediastinal neoplasm is rarely, if ever, a cause of significant pulse changes.

Survival is possible with slow obliteration of all the major branches of the arch. Symptoms include "visual claudication," dizziness or syncope on assuming the upright position, "claudication" in the arms, fits. Signs include, in addition to absent or diminished pulses, cataract, atrophy of the facial structures, loss of the nasal septum, ischemia of the ocular fundus, optic atrophy, and development of a corona of collateral vessels around the optic disk, masticatory "claudication," hypertension in the legs probably secondary to cerebral ischemia. A continuous murmur, identical to that of patent ductus arteriosus, has been heard at the base of the neck and over the upper chest in certain of the patients with full-blown changes. Myers *et al.* (140) provide the plausible explanation that the continuous murmur results from the fact that arterial pressure proximal to the obstruction is higher than that distally at all times in the cardiac cycle.

Treatment has included: (*a*) reaming out of the occluded ostia, and (*b*) grafts between the aortic arch and an unaffected portion of the branch vessels (134). Total replacement of the arch is within the realm of surgical practicability (41a, 123).

The Leriche syndrome.—(Thrombotic obliteration of the aortic bifurcation.) This disorder is almost always the result of atherosclerosis, to which

the bifurcation is particularly prone. All aortic thromboses occur with increased incidence in patients with hypercholesterolemia. It is, therefore, not surprising that a familial incidence of the Leriche syndrome has been described (88, 134). The Leriche syndrome occurred (134) in association with pseudoxanthoma elasticum, a heritable disorder of connective tissue in which premature calcification and obliteration of peripheral arteries occurs.

The syndrome is not infrequent in the 30's and 40's and occurs predominantly in men. Symptoms include (*a*) thigh and particularly buttock pain (22, 50) which may be interpreted as sciatica or some sort of orthopedic disorder related to the low back or hip, and (*b*) impotence (inability to maintain a stable erection). Signs include, in addition to absent femoral pulses (*a*) globose atrophy of the buttocks and legs which may be difficult to evaluate because it is symmetrical, and (*b*) by x-ray, especially lateral lumbar spine films, calcification in the terminal aorta. Aortography provides detailed information about the lesion but is usually not essential to the diagnosis. Thrombosis occasionally extends proximally to involve the renal ostia and leads to death (102).

Resection of the thrombosed bifurcation and replacement by a graft has been a highly satisfactory form of therapy (45). In 1954, Luke (120) was of the opinion that thromboendarterectomy is preferable when marked calcification is not present and the patient is under 60 years of age.

Saddle embolus.—[Embolus to the bifurcation of the aorta (118).] This accident occurs mainly with atrial fibrillation, mitral stenosis, or with myocardial infarction. Pain in the legs usually develops abruptly, but may build up insidiously in a bed-ridden patient. Signs of ischemia are always more dramatic than with the slow obliteration of the Leriche syndrome. Prompt recognition is important because embolectomy (21) may be highly successful if done in time (164, 192), preferably within 8 hr., although cure has been effected as late as 23 hr. after the accident. If unrecognized, loss of limb may occur or the Leriche syndrome may develop.

Coarctation

Variants.—Anatomic variations and pathologic changes in coarctation are surveyed by Clagett, Kirklin & Edwards (33) and Marston, Bradshaw & Meredith (127). Patent ductus arteriosus was associated with coarctation in 13 per cent of 118 cases (79) and 16 per cent of 1,187 cases (172). Additional cases of coarctation at unusual sites in the aorta are described (93, 96, 105, 108). Abrams (1) notes that rather frequently retrograde brachial aortography in infants may demonstrate slight narrowing at the aortic isthmus with distal dilatation. A nonobstructive distortion of the arch in the region of the isthmus is described under the various names of kinked aorta (28, 52, 186), buckled aorta, atypical coarctation, subclinical coarctation (178), pseudocoarctation (179). It may be associated with

aneurysm of the sinus of Valsalva (179). A shadow on x-ray taken for neoplasm or a systolic murmur (28) may prompt medical investigation.

Clinical aspects.—Campbell & Baylis (32) and Cleland *et al.* (35) have reviewed the natural history of coarctation after infancy. In one-fourth of the cases studied there was mild aortic regurgitation (32), the number increasing with age. Atherosclerosis in a congenital bicuspid valve was believed to be the basis. Aortic stenosis, often calcific (177) was present in about 5 per cent (32). An inconstant mid-diastolic apical murmur was heard in 15 of 40 cases (35). Wood (194), who heard it in a third of his patients with otherwise uncomplicated coarctation, ascribed the murmur to fibroelastosis of the ventricle with valve involvement. Oppenheimer (142) reported cases of fibroelastosis with coarctation.

Sandifer (162) found a normal brachial blood pressure in 6 cases. Kuhn *et al.* (111) re-examined the use of indirect femoral and radial pulse tracings in diagnosis.

The association of pregnancy and coarctation was reviewed by Pritchard (151) and Rosenthal (160). Rupture of the aorta occurred in 6 per cent of the reported cases (42), a further example of an increased incidence of aortic rupture in pregnancy. With proper care pregnancy is well tolerated in most cases (81, 86), however. Toxemia is virtually unknown in pregnant women with coarctation (42, 86).

Transplantation of kidneys to a site in the neck proximal to a coarctation (produced experimentally in dogs) provides data which Scott *et al.* (169) convincingly present as evidence for a renal factor in the hypertension of coarctation.

Surgical therapy and results.—Indications for resection are reviewed by Sealy (170) and by O'Sullivan & Glenn (144). The gross operative mortality rate—up to three weeks after surgery—was 8.6 per cent in 1601 cases reported by 36 surgeons (172): Mortality was highest in patients younger than 3 years and older than 30.

The special problems of medical and surgical management of coarctation in infants is discussed by Mustard *et al.* (139), Gerbode *et al.* (70), Gruner & Herbst (84), Minor *et al.* (137), Lang & Nadas (113), and others (193).

Postoperative necrotizing panarteritis indistinguishable from periarteritis nodosa and limited to arteries arising below the coarctation seems to have been reported first by Sealy (170). At least 5 fatal cases and numerous nonfatal presumptive cases are described (16, 35, 83, 90, 117, 148, 155). Sudden rise in intravascular pressure may be a factor. Clinical manifestations include abdominal pain, vomiting, and signs of inflammation appearing 3 to 7 days after operation. The picture may be that of fever of unknown origin; bacterial endaortitis may be feared. Infarction of bowel with perforation has occurred. Paradoxical elevation of diastolic pressure after operation may be related (171). A frequency of 10 (83) to 30 per cent (155) has been given.

Counihan (37) and Wright *et al.* (195) observed the blood pressure after resection of coarctation. Slight residual elevation of blood pressure was found in many, although slow continuing fall of pressure occurred after the immediate postoperative period. Of 1230 patients reported by 36 surgeons (172), hypertension persisted after operation in 4.7 per cent. It was reduced, though not to normal, in 23.2 per cent. The duration of follow-up was not specified.

Other Anomalies of the Thoracic Aorta

Anson (4) reviewed the normal variations in the branching of the aortic arch. For lack of space review of the large literature dealing with patent ductus arteriosus and aorticopulmonary septal defect will be omitted.

Embryology and anatomy of "vascular rings" has been considered by Edwards (58). Gross (82) examined the clinical manifestations and results of surgical therapy in 70 cases. Anomalies encountered in descending order of frequency were (*a*) double aortic arch; (*b*) right arotic arch with left ligamentum arteriosum; (*c*) anomalous innominate artery (arising more distally than usual); (*d*) aberrant right subclavian (arising from the distal aortic arch); and (*e*) anomalous left common carotid artery (branching from the aorta more proximally than normal). A double arch may remain asymptomatic (82, 201), as usually does right-sided aortic arch which occurred as an isolated finding in 6 adults in a group of 20,000 consecutive minifilms (23b). Naylor (141) discussed vascular rings in dogs.

Mannix & Haight (126) have reviewed the syndrome of congenital lung cysts and anomalous pulmonary arteries arising from the aorta.

Miscellany

Marked calcification of unknown cause was described (153) throughout the aorta of a 25-year-old woman. The blood pressure was 210/60 mm. Hg. Ross & McKusick (161) described what appears to be a similar case in a 33-year-old woman (E.L.). The blood pressure was 65/45 mm. Hg in both arms, caused apparently, by stenosis of the ostia of branches at the arch.

Conway & Smith (36) suggest amyl nitrite as a test of elasticity of the great vessels including the aorta. In the period before tachycardia, the absence of reduction in pulse pressure with the fall in diastolic pressure appears to indicate a normally elastic arterial tree.

After other causes of dysphagia have been excluded, there are left occasional cases (106), usually elderly hypertensive women, in whom a markedly elongated, tortuous and sclerotic aorta which "carries the esophagus with it" appears to be responsible.

Crawford & Levene (40) studied atheromatous aortas fixed under pressure and concluded that medial thinning is a primary feature. Atheromata are minute shallow aneurysms; in life the plaque may not project into the

lumen but rather occupy a depression resulting from the medial thinning.

It has never been conclusively proved that specific therapy prolongs life in cardiovascular syphilis (3). There is no convincing histologic evidence that penicillin influences established syphilitic aortitis (176, 184). The incidence of aortic regurgitation may be higher in syphilitic aortitis, and the prognosis after its development better, than previously thought (97, 121).

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CARDIOVASCULAR DISEASES (SURGICAL)[1]

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It would be difficult to define the stimulus which has produced the tremendous interest and advancement so noteworthy in surgery of the heart and blood vessels during the past five years. The atmosphere for such advancement was provided by excellence of anesthesia methods, the availability of the anticoagulant heparin, and by the antibiotic drugs. The sudden fruition of years of work by many on pump-oxygenator methods has been the most recent major development in heart surgery, while the demonstration of the practicality of a wide variety of blood vessel grafting procedures has been fundamental to the present state of blood vessel surgery. The fact that the promise of the field has attracted many new individuals in clinical and laboratory medicine and surgery is no doubt the best explanation for its rapid development.

The basis for this report is a review of the major cardiovascular literature during a period of somewhat over a year prior to its submission. This period has been characterized by refinements in technique, and extension of indications for use of various techniques rather than by the addition of any fundamental method in either heart or blood vessel surgery. In blood vessel surgery, the use of vascular grafts and the refinement of prostheses has continued. Extension of vascular replacement to the hitherto inaccessible thoraco-abdominal region of the aorta and the aortic arch was an outstanding milestone. Various applications of direct surgical techniques previously developed in the larger arteries to the coronary arterial system indicate that the future of surgery in this direction is as promising as it has proven in the case of the larger vessels. In intracardiac surgery, increasing confidence in methods of complete cardiac by-pass has prompted its use in a number of centers for the correction of lesions which previously have been more or less successfully cured by less spectacular means. The thoroughness of correction gained by the use of a pump-oxygenator in such lesions has been the reason for this application. The phenomenal is becoming commonplace, and the most active workers in the field are beginning to eye the completely impossible.

Patent Ductus and Coarctation of the Aorta

With modern pre- and postoperative management and good anesthesia, the surgery of uncomplicated patent ductus has become a routine procedure.

[1] The survey of the literature pertaining to this review was concluded in November, 1957.

Division and suture of the lesion rather than simple ligation is widely insisted upon. The safety of the procedure is characterized by the report of Glenn *et al.* (1) of 110 operations on patent ductus arteriosus without a mortality. In the 108 patients upon whom the 110 operations were done, subacute bacterial endocarditis had been suspected preoperatively only in three. Eleven per cent of the patients were 18 years of age or older, while females outnumbered males 3½ to 1. It is of importance to note that other congenital heart and great vessel defects were present in 22 of these patients. The diagnosis was sufficiently difficult in 36 to require catheterization. Seventy-two of the patients showed residual murmurs after surgery. Potts *et al.* (2), in reviewing the causes of death in 1000 operations for congenital heart disease, reported 347 instances of patent ductus in which there was no mortality.

Davis *et al.* (3) and Mozen (4) have encountered other lesions simulating clinically a patent ductus arteriosus. Davis reports the discovery and repair of an aorticopulmonary fistula in a four-month-old infant which was cured by ligation alone. His second case remains unsolved. In this instance he successfully repaired a patent ductus in a three-year-old girl with persistence of a continuous murmur over the right chest. When the right chest was explored, the cause of this patent ductus murmur could not be found. A third case was a very unusual instance of an abnormal left coronary artery draining into the right ventricle. This lesion was cured by ligation of the abnormal coronary artery branch. Mozen's report concerns an exactly similar congenital defect in a ten-year-old boy. Mozen calls the lesion a congenital cirsoid aneurysm. In this instance, the abnormal coronary artery emptied into the left atrium and was cured by ligation.

The problems concerned in the treatment of patent ductus arteriosus when it is complicated by pulmonary hypertension arise from the question as to whether it may be closed without producing right heart failure, and the technical problem of closure arising from the size and thinness of the pulmonary artery. Sirak & Humphries (5) operated on 10 patients with patent ductus and pulmonary hypertension with four deaths. Four major hemorrhages occurred during the surgery. Only one of these hemorrhages proved fatal. Sirak suggests the use of the clamp devised by Potts and Smith for aorticopulmonary anastomosis on the aortic end of the ductus in order to leave as much tissue as possible on the pulmonary end. In one patient who recovered, Sirak withdrew blood from the patient during a period of severe hypotension which he correctly judged to be due to heart failure rather than circulatory collapse. He did this because of a previous case who was given transfusions during hypotension and who died. His experience leads him to advise surgery in patients with complicating pulmonary hypertension. Ellis *et al.* (6) advised against closure of the patent ductus in patients with sufficient pulmonary hypertension to produce an exclusively right to left shunt, or one in which the right to left exceeds the left to right shunt. This was on the basis of a 50 per cent over-all mortality in 14 cases exhibiting

this much hypertension. Because of the danger in closing the thin pulmonary artery end of the ductus, Ellis has cross-clamped the aorta above and below the ductus in order to cut the lesion off flush with the aorta which may then be closed. The pulmonary artery end then benefits by having all of the ductus tissue for closure. Gerbode *et al.* (7) reported 11 patients with patent ductus and pulmonary hypertension of whom 10 were operated upon with complete closure at the expense of one death. From these various reports the impression is gained that the danger of closing the ductus in the presence of hypertension is about equally distributed between the hemodynamic change of a successful closure and the danger of doing the procedure.

The occurrence of postoperative abdominal pain after repair of a coarctation of the aorta has often been noted. Ring & Lewis (8) and Cleland *et al.* (9) have remarked on its incidence. Sealy *et al.* (10) noted the coincidence of paradoxical hypertension with the occurrence of postoperative abdominal pain. Sealy studied 30 patients in whom the postoperative blood pressure records were adequate for the purposes of his review. Seven of these patients showed an immediate paradoxical elevation of the blood pressure above preoperative levels. Fourteen developed a hypertension after an initial period of blood pressure drop. In these cases, which he calls delayed paradoxical hypertension, the diastolic pressure was significantly elevated above the preoperative levels. It lasted six to fourteen days and was longest in one of two patients who developed patchy gangrene of the small bowel requiring laparotomy and resection. In six patients, postoperative abdominal pain was associated with diastolic hypertension. He believes the immediate onset of hypertension is due to a disturbance of the pressor receptors in the carotid arteries and the aorta, while the delayed type is apparently initiated by severe vascular spasm, particularly marked in the abdominal viscera, which may progress to vascular degeneration and obstruction leading to necrosis of the bowel. In his studies of patients showing a paradoxical rise in blood pressure, and having abdominal pain, it was noted that the pain disappeared when the blood pressure was brought down with hydralazine hydrochloride infusions.

Keeley & Wyant (11) reported benefit from the use of a controlled hypotension with trimethaphan (Arfonad) in three cases of coarctation resection. They mention that the dissection of the lesions appeared to be easier, and that clamp application was less traumatic during reduced blood pressure.

Surgery of the Heart Valves

Operations for mitral stenosis were the first intracardiac operations to be done, largely because the approach to the mitral valve is relatively simple. In some respects this may be unfortunate because the very simplicity of approach has led to an almost too wide application of surgery for mitral stenosis. It is undoubtedly true that a large portion of patients with this lesion are operated upon without sufficient preoperative study and without the specific technical training of the surgeon which is necessary for a

maximum chance of a superior result, if the valve happens to be difficult or the atrium clot-filled or otherwise presenting technical difficulties.

An emergency during mitral commissurotomy occurs when the left atrium occasionally is torn. A simple method of controlling the torn atrium has been developed by Morris & Haight (12). They introduce a 20 ml. Foley catheter into the left atrium through the opening which has been made for finger introduction, inflate it, and pull it up against the inner surface of the tear. The traumatized portion can then be repaired, and the interrupted sutures are carried on up over the original atriotomy incision before the catheter is deflated and removed.

Most surgeons open the mitral valve by a finger fracture in preference to application of the valvulotome because of the danger of producing mitral regurgitation through a misplaced valvulotome incision. Through the development of a thimble valvulotome, Glenn (13) offers an improvement of the efficiency of the finger fracture method without the use of a cutting edge. He describes the method developed during his last 100 operations, using a thimble-like sleeve for the distal phalanx of the index finger which is worn under the glove. This thimble increases the efficiency of the stress applied by the finger on the adhered commissures by its rigidity and by the traction supplied by roughness of its surface.

Of greatest interest is information concerning the late effects of this operation which has been applied for longer than five years. Glover (14) has evaluated the effects of mitral commissurotomy on a series of 50 patients observed for five to six and a half years after operation. Of the original 50 patients, three died postoperatively, two of valvular insufficiency and one of surgical shock. Six patients died within three years, and 41 remained living five years or more. The important conclusion from his study was that the degree of clinical improvement obtained at the end of the first postoperative year was maintained almost without exception over a five-year period.

The infecting organism was staphylococcus in 10 of 12 cases of bacterial endocarditis following cardiac surgery in a series reported by Koiwai & Nahas (15). In this series which includes 1190 patients with an over-all incidence of 1.01 per cent, surgery of the mitral valve accounted for four instances and of the aortic valve for six. The actual incidence in mitral valve surgery was .47 per cent and in aortic valve surgery 3.84 per cent. In an unrecorded number of these operations, the ungloved finger was used by the surgeon.

Mitral insufficiency is a more devastating lesion than mitral stenosis and is a much less satisfactory surgical problem. An attempt at a homotransplantation of a functioning valve is reported by Pollock & Thomas (16), who placed homograft tricuspid valve cusps in 10 dogs. They found that the valves healed well to the host but soon became degenerative and nonfunctioning. They conclude that little is to be expected of such attempts until the two factors of antibody reaction and avascular degeneration of

transplanted tissue are overcome. Glover & Davila (17) report results of 27 operations for mitral insufficiency by the pursestring technique. They note that mitral insufficiency is caused by the contracture of the mitral leaflets, shortening of the chordae, and enlargement of the ring. They tried to overcome this latter factor in 27 patients by passing a heavy pursestring suture around the exterior of the left atrium at the level of the atrioventricular ring and claim some success for the method. Bailey (18) describes the results of 12 operations for mitral regurgitation in which he plicates the regurgitant end of the valve with interrupted sutures. In these he noted the abolition of the regurgitation in one-half of the patients and a significant reduction in the remainder.

Numerous previous reports of operations on the aortic valve for stenosis have recorded the development of transventricular introduction of a valve dilator. The next method has been introduction of a valve dilator or the finger through the aorta above the valve through a temporary diverticulum sutured to the ascending aorta. As a natural corollary to open surgery on the pulmonary valve, the University of Illinois group (19) reported on two cases of aortic valvulotomy under direct vision during inflow cardiac occlusion and hypothermia. This same approach was studied experimentally in dogs by Adam (20). The dog's body temperature for this procedure was reduced to 28°C. In the experimental work, Adam and his co-workers passed a polyethylene catheter into the left ventricle through the myocardium in order that a steady flow of saline solution could be allowed to enter the left ventricle, washing blood from the ventricle cavity, and making the valve cusps visible through the clear solution without exposing the coronary orifices to potential air embolism. Air embolism was eliminated in this experimental work. Swan & Kortz (21) and Lewis *et al.* (22) have reported also on the clinical application of this method. Swan describes a successful clinical case in which the aortic valve was incised along the commissures during an occlusion time of 6¼ min. Lewis reports three cases being done under the hypothermic range of 28° to 31°C. Air embolism was not a troublesome factor in these cases, or in those reported by Julian (19), if strict attention was paid to the avoidance of plugging the aortotomy wound with finger or instrument while any air remained in the ascending aorta.

The use of a rigid plastic valve, developed by Hufnagel for implantation into the descending aorta in aortic insufficiency, is admittedly a method of temporary value. Operations devised to narrow the size of the aortic valve ring have not found wide acceptance, and undoubtedly the next important step in surgery of aortic insufficiency will be the development of a long-lasting prosthesis which may be placed in the aortic valve ring proximal to the coronary ostia. A flexible aortic valve prosthesis, satisfying some of the requirements, has been developed and tested by Roe *et al.* (23). This experimental study shows great ingenuity in that the valve is introduced through an incision in the descending aorta and drawn into place by a

previously placed "fishing loop" which was introduced at the valve ring. By this maneuver, it is possible to bring a prosthetic valve into place without opening the base of the aorta. This artificial valve is constructed of polyvinyl plastic and showed very little resistance to unidirectional flow with excellent competence to retrograde pressure of 220 mm. of mercury. The obvious objection raised by the investigators was that the coronaries would of necessity be subjected to systolic rather than diastolic filling until a similar valve could be brought into place proximal to the ostia. The use of the Hufnagel valve in aortic insufficiency complicated by mitral insufficiency has been tested out hemodynamically on dogs in whom both aortic and mitral insufficiency were produced. These experiments by Roshe and his co-workers (24) showed that this dual lesion was poorly tolerated by a dog, and that if the Hufnagel valve were inserted in the descending aorta, the mean left atrial and left ventricular end-diastolic pressures were both reduced. It was concluded that the patient with such a double lesion may benefit by a Hufnagel valve insertion.

The open method of surgery for valvular pulmonary stenosis under hypothermia has attained wide use as giving more secure results and not being subject to failure of the valvulotome to cut the valve rather than simply to distend it. Himmelstein *et al.* (25) has devised a new valvulotome for closed pulmonary valvulotomy which has a positive cutting action and, if properly used, cannot give disappointing results through distention of a small, but somewhat elastic valve orifice. In their clinical work with this instrument, they obtained excellent results in four of eight patients by paying meticulous attention to the pressure gradient during surgery before and after the incisions had been made. The new valvulotome cuts from above in a scissors-like action, and can be applied to two or three points in the valve circumference. In the four patients attaining an excellent result, the gradient postoperatively was less than 20 mm. of mercury. In two patients the gradient was less satisfactory, being between 20 and 40 mm. of mercury. One patient had an infundibular diaphragm which was not successfully repaired.

Gott *et al.* (26) report the experience of the Minnesota group in treatment of lesions at the root of the aorta using the pump-oxygenator plus coronary perfusion. The cases included aortic stenosis and, of the three patients who died, of the total of seven operated upon, one diagnosis was a transposition, one was an aortic septal defect, and only one was a calcified aortic stenosis. By perfusing the coronary arteries through the aortic base at the rate of 25 to 55 cc. per min., it was found that 15 to 20 min. of open aortic surgery could be tolerated.

Intracardiac Septal Defects

It has been adequately demonstrated that interatrial septal defects may be repaired by three major kinds of procedure. One major class is the closed or "blind" method for which several methods are available. Closure

by open methods is accomplished in two major ways. Many such defects can be closed through the use of hypothermia, and the pump-oxygenator is available for closure of the more complicated defects. In order to plan the surgical procedure in any individual case in a direct, straightforward manner, it is desirable to determine the method of procedure prior to surgery. This has not always been done and Lam (27), early in his work in atrial septal defects, was frequently able to make the transition from a closed method to a method under hypothermia when he found a defect that could not be closed from the exterior of the heart. In these cases he simply made a temporary closure of the chest and waited for hypothermia to develop under application of cold. The transition from a closed method, or hypothermia method, to the heart-lung machine would be even simpler, except for the effort which must be made by the blood banks of the institutions to have the pump-oxygenator in readiness for possible use.

A modification of the Sondergaard technique for the closed repair of interatrial septal defects has been developed by Bosher (28). In addition to the circumclusion suture which he places in the usual manner, Bosher passes two to three sutures through the defect from the posterior surface of the heart. These are placed easily with a relatively small needle after the circumclusion suture has been brought down almost to closure. He has applied this method to 11 patients with satisfactory results. Bolton *et al.* (29) closed 100 cases by atrioseptopexy. Of these, 83 were of the ostium secundum type and 17 had ostium primum defects. It is notable that 12 of the total of 25 deaths occurred in the 17 patients having the primum defects. Thirteen deaths occurred in the secundum cases, and eight of these were in nine patients who had balanced shunts due to pulmonary vascular changes. Bolton and his co-workers report that there is no difficulty attendant upon the frequent association of aberrant pulmonary veins when the secundum type defect is posteriorly placed. They conclude that the indication for closure of an atrial septal defect probably should be absolute if the defect is of the secundum type. In a review of 34 cases, Longmire *et al.* (30) compared three of the current methods of closure. They closed 11 using the atrial well, 15 with atrioseptopexy, and four by an open technique with hypothermia. In two instances in each of the closed methods, the defect was not completely closed, and there were two deaths attendant to the use of the atrial well. Neither mortality nor partial failure occurred in any of the open cases. Kirklin, Ellis & Wood (31) described in detail the operative method used in repairing atrial septal defects complicated by aberrant pulmonary veins in six cases. Of the four in which the repair was complete, two were done with the well and two with atrioseptopexy. Their report indicates the ingenuity which is sometimes required when repair of this lesion is attempted by blind methods.

Total anomalous pulmonary venous drainage presents a different mechanical problem. Rowe, Vlad & O'Hanley (32) examined 58 cases in which all the pulmonary veins had an anomalous drainage into the venous

atrium. Their report in 1954 showed that in 53 instances all the veins entered one common channel which then, most commonly, drained into a persistent left superior vena cava. They described the characteristic "snowman" appearance which is seen on x-ray. This anatomical description was the basis of the surgical technique applied by Mustard & Dolan (33) to 12 patients. These authors connected the left atrium to the left superior vena cava and then, in some instances, partially ligated or ligated the aberrant vena cava above the anastomosis. In their series of 12 patients, who were three weeks to seven years in age, there were eight deaths.

Hypothermia

Methods of prolonging the period of circulatory arrest under hypothermia and of increasing its safety have shown a good deal of promise. If the stimulus to this work is not entirely removed by substitution of cardiac by-pass techniques, hypothermia could undoubtedly by intensive study be extended to application in even the most complicated cardiac defects.

Niazi & Lewis (34) produced deep hypothermia in the dog and were able to produce 17 survivors out of 21 dogs in which inflow occlusion was carried out for 30 min. at 17°C. There was no brain damage in these dogs. Adding right ventriculotomy to the 30 min. of occlusion in nine dogs at 18°C. produced 100 per cent survivors. Kimoto *et al.* (35) selectively cooled the brain by perfusion. One carotid artery was exposed, and inflow and outflow into a coiled heat exchanger resulted in a fairly even cooling of both sides of the brain. The brain temperature dropped to about 15°C., while the rectal temperature dropped only to 32°C. Following this experience with the experimental animal, these authors have used the method in five clinical cases, principally atrial septal defects. Occlusion time up to 13 min. was survived but occlusion of 20 min. was followed by death from "anoxia."

These reports indicate that profound hypothermia or selective cooling of the central nervous system could be established to allow for longer periods of circulatory occlusion for more complicated intracardiac procedures. The second difficulty with hypothermia is the development of abnormal rhythms frequently observed during hypothermia.

The therapy of ventricular fibrillation under hypothermia was studied by Kay & Gaertner (36). Dogs were cooled to 25 to 32°C., and caval occlusion was carried out from 8 to 29 min., during which time various procedures were done. In one group of the longer occlusion times, coronary and carotid perfusion was carried out. A high proportion of these dogs developed ventricular fibrillation during or immediately after the caval occlusion. Some were defibrillated using manual systole for several minutes and then the application of 130 v. for a quarter of a second. If this failed, they all finally did respond when 2 to 3 cc. of 1:10,000 epinephrine hydrochloride solution was injected into the left ventricular cavity, cardiac

massage carried out for 2 or 3 min., and then electric shock applied. The group at the University of Indiana studied the problem of ventricular fibrillation and coronary air embolism under hypothermia. They found that the procedure of Geoghegan and Lam, in which the aorta is cross-clamped and manual systole carried out to push air emboli through the coronary system, sometimes failed. At this point of failure, Riberi and his co-workers (37) cut the terminal end of the embolized coronary artery and were then able to milk the air out of the vessel and re-establish sinus rhythm. The incised coronary was closed with a transfixion suture. The effectiveness of potassium chloride and of electric shock in the fibrillating ventricles of a hypothermic dog was compared by Kyle & Kirby (38). Dogs under pentobarbital anesthesia were cooled to 27°C. and then usually fell approximately 2 degrees more. Fibrillation was induced by direct application of 10 v. of electric current for half a second. The ventricular fibrillation was allowed to continue for 4 min., and then manual systole was started at 80 per min. Five m.eq. of potassium chloride in 5 cc. was then injected into the aorta proximal to an occluding clamp, and the heart was compressed 15 times. The same procedure was then carried out on a second group of animals using electric shock rather than the injection of potassium chloride. Under these circumstances, it was found that both electric shock and potassium chloride were 100 per cent effective in defibrillating the heart. However, potassium chloride was followed by effective contractions and sinus rhythm in only 57 per cent of the cases, while electric shock was followed by a good heart beat in 100 per cent of the cases. The Philadelphia group also reports the use of sodium lactate in patients showing an abnormal rhythm secondary to hyperkalemia (39). Previous reports of the effectiveness of this solution prompted them to use it in two patients having severe bradycardia as a complication of the intracardiac surgery. Each patient had a slow, ineffective heart beat and was distinctly improved by the infusion of one molar sodium lactate. One patient showed an ineffectual bradycardia after restoration of normal rhythm in a ventricular fibrillation occurring as an interatrial septal defect was being repaired under hypothermia. Atropine and epinephrine were not effective in speeding up or strengthening of the heart action before the lactate was given. The second patient was also one in which a slow rhythm was present following recovery from ventricular fibrillation with electric shock.

Spencer *et al.* (40) used coronary perfusion and also regulation of carbon dioxide in the alveolar air during intracardiac procedures performed under hypothermia. The 29 operations consisted of 12 atrial septal defects, eight pulmonary valvulotomies, four aortic valvulotomies, two infundibular resections, and one correction of a total anomalous pulmonary venous drainage. The coronary perfusion was carried out at a rate of 15 to 70 cc. per min. by gravity through a needle introduced proximal to a clamp on the ascending aorta. Occlusion time at a body temperature of 32 to 33°C. was

2 to 12 min. The patient who was occluded for 12 min. died. There were six other deaths in the 29 operations, four of which were complicated by ventricular fibrillation.

An important consideration in resuscitation of the arrested or fibrillating heart is pointed out by Adelson (41) who studied at autopsy the damage which resulted to the heart in 60 cases of cardiac massage. He found all degrees of damage including six (10 per cent) instances of gross laceration of the myocardium. A hopeful aspect of his report was the fact that in some hearts, in which massage had been carried out for one hour successfully, there was no damage.

An explanation of the occasional hemorrhagic diathesis which accompanies hypothermia was sought by Ellis, Kleinsasser & Speer (42). These workers noted the disappearance from the circulating blood of several measurable elements of the clotting mechanism (proaccelerin, proconvertin, prothrombin, and fibrinogen) during hypothermia at 26 to 29°C. for 2 hr. The important observation was the fact that the administration of 3 mg. of heparin per kilogram at the onset of cooling minimized this depression. They concluded that the effect of heparin was to prevent diffuse, small areas of intravascular clotting during the cooling period, thereby preventing the depletion of the coagulation substances studied. They encountered no instance in which the heparin itself produced hemorrhage.

Two suggestions have been made regarding the management of ventricular fibrillation occurring as an unexpected catastrophe not associated with cardiac surgery. Zoll *et al.* (43) reported the external application of electric shock in four patients. The shock was of a magnitude of 240 to 720 v. and produced successful defibrillation. Only one patient survived, one with Stokes-Adams' syndrome whose fibrillation was successfully combatted by this method on three occasions. In the three patients who died, the ventricular fibrillation had been present for more than 7 min., and the authors note that recognition is a major problem. Bencini & Parola (44) devised a cannula which can be placed in the pericardium, much as the air valve is placed in an inner tube, through which "pneumomassage" of the heart can be carried out very effectively. Practical application of this method seems to be problematical because of the time required to place the instrument, but the mechanical effect was apparently excellent.

Open Heart Surgery with Cardiac By-Pass

There is rapidly expanding use of total cardiac by-pass, using a pump-oxygenator of one type or another. The principle of bubble oxygenation of the extra-corporeal blood, which has been brought into its present reliable form by DeWall & Lillehei, is the most widely used. DeWall *et al.* (45) have recently published extensive experimental studies which detail the effect of this method of oxygenation on the physical, chemical, and oxygen-bearing qualities of the perfused blood. In 70 animals, perfusion for 30 min. at 16 to 50 cc. per min. per kilogram perfusion rate resulted in immediate

recovery of 48 animals without evidence of neurological damage. Ten animals suffered neurologic injury but recovered in one to five days, and 12 were sacrificed or died, all being subject of neurological damage. They stress again the importance of the helix reservoir, having compared it to a vertical collecting chamber in nine experiments. In all of these animals except one there was neurologic injury to the animal which they attribute to the ineffective floating off of very small bubbles in a chamber of this type. They also stress the necessity of smooth connections and the need for an effective atraumatic filter. The same group (46) studied the use of donor blood arterialized by warming the arm and hand of the donor during drawing blood and the breathing of 100 per cent oxygen during this period. The majority of samples drawn in this way were 90 per cent saturated. This blood was used in three cases using a reservoir technique of perfusion, and in 59 cases blood drawn in this fashion was used to prime the bubble oxygenator. The oxygen content and other chemical characteristics of such arterialized blood was considered to be superior to venous blood for this purpose.

Several reports adding to the details of cardiac by-pass in repair of specific defects other than interventricular septal defects have been published. Kay & Cross (47) concluded, on the basis of their own experience and the reported experiences concerning transposition of the great vessels, that the transposition ought to be on the venous inflow side rather than by direct approach to the transposed arteries. Kay devised a procedure which was carried out under total cardiac by-pass. A plastic procedure is done on the right atrial wall producing complete transposition of the venous inflow. He has operated on two patients, 19 months and three years of age, both with technical success but both terminating in fatality actually unreleated to the successful procedure except possibly to the length of time in which the by-pass was used. Cooley *et al.* successfully repaired a ruptured interventricular septum (48). He also repaired three aorticopulmonary septal defects, one of which was done with pump by-pass (49), and reported six patients with common atrioventricular canals (50). The repair of the ruptured interventricular septum following acute myocardial infarction offered small difficulty from a surgical standpoint, but terminated fatally six weeks postoperatively because of complications. Cooley, Kirklin & Harshbarger (50) of Rochester, Minnesota, provided useful descriptions of the deformities of the mitral and tricuspid valves seen during repair of common atrioventricular canals in nine patients. Six of these were done under direct vision with cardiac by-pass and, in four, mitral insufficiency was seen. The actual cleft of the mitral valve was clearly visualized, and in one instance it was sutured. The septal defect itself was closed in each instance using a 4 mm. thick, noncompressed Ivalon sponge. The importance of repairing the mitral valve when it is badly deformed is illustrated by the fact that one of the two deaths was in a patient who had an unrepaired cleft and died of unrelieved mitral insufficiency. Lam *et al.* (51) utilized

acetylcholine to produce elective cardiac arrest during 100 open heart surgical procedures. Their report indicates that cardioplegia did not contribute to the over-all 30 per cent mortality which occurred in 58 interventricular septal defects. The strong influence of age of the patient was stressed, in that in 14 repairs done in patients under the age of one year nine were dead; of 44 over one year 11 were dead; five deaths occurred in 22 patients over two years; while only one of the deaths occurred in a group of 21 over the age of three years. Four tetralogy of Fallot lesions were included in this series of 100, all succumbing to the operation. Cooley, Latson & Keats (52) of Houston, Texas, use potassium-induced cardiac arrest by the Melrose technique in cases of interventricular septal defect. This group has developed a stainless steel oxygenator of the bubble diffusion type, having a vertical collecting chamber, which they have used without air embolism.

Excellent results are being obtained in a variety of clinics using disk, and screen types of oxygenators in the cardiac by-pass apparatus. Cross & Kay (53) use a rotating disc apparatus utilizing 59 silicone coated stainless steel discs which rotate from a blood reservoir into an oxygen to 1½ per cent carbon dioxide atmosphere. Forty-five cases in which this was used were reported with a 27 per cent mortality. This mortality is correctible to 23.2 per cent with the abolition of two cases of inoperable transposition of the great vessels. Kirklin and his group at Rochester, Minnesota, expressed satisfaction in the use of a modified Gibbon screen oxygenator (54). Sealy *et al.* (55) have added hypothermia and controlled cardiac arrest for open heart surgery using a low flow extracorporeal circulation. In seven patients, the rectal temperature was reduced to about 35°C. with ice and subsequently drifted to 30 to 31°C. One of these patients had, in addition, an induced cardiac standstill using potassium, and at the time of publication of their article the authors reported 11 additional patients including five more in whom arrest was induced without ventricular fibrillation. Plastic bag oxygenators previously reported by the same workers were used for the low flow perfusion.

Pulmonary hypertension resulting from acquired changes in the pulmonary arterial circulation would at the moment seem to be the limiting factor in many instances of interventricular septal defect and, to a lesser degree, in atrial septal defect, patent ductus, and aorticopulmonary septal defects. Dammann, Baker & Muller (56) studied this problem through the experimental production of pulmonary arterial hypertension in a portion of the pulmonary circuit. The hypertension was produced in the left upper lobe of the dog lung by end-to-end anastomosis of the left subclavian artery to the pulmonary artery branch. They followed histologically the full development of pulmonary arteriolar change over a period of only 11 weeks. At this time the changes were as advanced as are seen in some clinical cases. Studies as to the reversibility of the phenomenon are now possible on the basis of this work.

Edwards & Burchell (57) made a critical examination of the essential lesion producing an aneurysm of an aortic sinus and its method of rupture into cardiac chambers. Sawyers, Adams & Scott (58) reviewed the aortico-atrial fistulae resulting from rupture of such an aneurysm of a sinus of Valsalva into the atrium. Such aneurysms are reported to have been congenital, syphilitic, and bacterial. The congenital ones result from a developmental weakness of the aortic wall above the annulus fibrosis of the valve. They were able to find 47 reported cases since the original description of the lesion in 1840. Experimental fistulae were produced in dogs, and it was found that fistulae up to 3 and 4 mm. were tolerated by the dog, while those between 5 and 10 mm. produced death within 10 days. They devised an experimental method of closure of the fistula using hypothermia and inflow occlusion, repairing the defect through the opened atrium, sometimes using a guiding finger placed into the aorta through an artificial appendage. Baker (59) produced experimental cardioaortic fistulae, and then repaired them using a very interesting appliance made of Ivalon sponge. The sponge was compressed and shaped to resemble a golf tee and then passed by ligature to plug with its button-end the aortic end of the defect.

Operations for Coronary Insufficiency

A variety of surgical procedures to bring new blood supply to the ischemic myocardium have been tested experimentally, and a surprising number have immediately been subjected to clinical trial.

The Vineberg type of procedure, in which the mammary artery is implanted into the myocardium, was evaluated experimentally by Maniglia & Bakst (60). Nine animals were used and six months later the arteries that had been implanted were found to be severely narrowed or occluded both grossly and microscopically. The back flow from the anterior descending branch was measured to test the efficiency of the new vessel. It was unaffected by clamping the implanted internal mammary artery. They concluded that the Vineberg operation does not contribute to heart supply six months after implantation. Vineberg, however (61), has re-emphasized the necessity for artificially induced ischemia of the myocardium to stimulate formation of branches from the implanted vessel. Inasmuch as Maniglia did not produce such ischemia, the variation and results may be due to this difference in technique. Smith *et al.* (62), in a study of several methods of revascularization, substituted a small diameter, crimped nylon graft for the internal mammary artery in the Vineberg procedure. This graft was attached end-to-side to the aorta and then passed into the myocardium, several nicks being made in the wall of the graft to allow bleeding into the tract. In these experiments previous ischemia was not used, but nonetheless the authors claim that there was evidence of an auxiliary myocardial blood supply.

Beck (63) has drawn upon data obtained in 5000 experimental operations during 24 years. This has led him to a concept of coronary disease

having as its underlying theory an importance ascribed to oxygen differentials in various areas of heart muscle. Such differences in oxygen content lead to differences in electrocardiographic tracings and to instability with regard to ventricular fibrillation and cardiac standstill. The part that such a theory plays in the clinical aspects of coronary disease is described, and to some extent the theory explains the wide diversity of experimental procedures which seem to provide increased myocardial blood supply. Beck states that his procedure of arterialization of the coronary sinus is now abandoned because its lasting effect is due to the improvement in intercoronary circulation rather than to a continued arterial supply through the coronary vein. This can be achieved by a much simpler and safer surgical procedure.

A simple and possibly revealing experiment is reported by Siderys *et al.* (64). Three groups of animals were treated as (*a*) controls, (*b*) ligation of the great cardiac vein, and (*c*) simple pericardiotomy. The animals in all groups were tested for accessory coronary circulation by ligation of the anterior descending branch of the left coronary artery and by retrograde flow from the anterior descending branch. It is to be noted that coronary vein ligation and simple pericardiotomy equally protected the animals as compared to the control group. The conclusion was that a simple opening of the pericardium afforded sufficient protection, possibly through the mechanism of intercoronary connections, as to obscure the results of many experimental procedures. Baronofsky, Hannon & Turback (65) afforded protection from ligation of a left coronary branch by previously applying the denuded serosal surface of the jejunum to the surface of the heart in a two-stage experimental operation. The beginning of direct surgical approach to the occluded coronary vessel itself is seen in several reports and presents several hopeful features. Admittedly, the problem is made tremendously more difficult than is the problem in larger vessels of the extremity by the difficulty of a minute diagnosis by x-ray, the uncertainty of the distal run-off which will be present after a direct surgical repair has been made, as well as by the small size of the vessels. In spite of these problems, Absolon and his co-workers (66) have established the feasibility of doing endarterectomies on the coronary vessels of man by practice observations done on human cadaver hearts. These same investigators made anastomotic connections in dogs between the internal mammary artery and the left circumflex artery, the left carotid artery and the circumflex artery, and the subclavian artery and the circumflex artery. Using polyethylene shunts in some instances and the total cardiac by-pass in others, Julian and his co-workers (67) have produced long-term survivors in animals with anastomoses between the internal mammary artery and the circumflex coronary artery as well as between a homologous graft from the ascending aorta and the left circumflex coronary artery. Bailey (68) has made an early clinical trial at direct surgery on the coronary vessels by doing a thromboendarterectomy of the anterior descending branch of the left coronary artery in man.

It seems more likely that great success will be attendant on direct surgical procedures on the coronary vessels than that long-term good results will come from the indirect methods. It is entirely possible, however, that even the best graft procedure or thromboendarterectomy will be applicable to only a small proportion of coronary patients who satisfy rather rigid requirements.

Acquired Lesions of the Thoracic Aorta

Very significant information concerning the blood supply to the spinal cord which may be a limiting factor in treatment of many lesions of the thoracic aorta was provided by Adams & Van Geertruyden (69). Their collection and study of instances in which the thoracic aorta has been clamped provided 24 cases of ischemia of the spinal cord. It was noted that the spinal cord was never damaged with infrarenal clamping of the aorta because of the absence of branches below this level, or because there is good collateral circulation to the cord even if it is sometimes additionally supplied from below the renal level. Cord damage is likely to occur only from obstruction of the aorta below the subclavian artery and by procedures which require ligation of the lower thoracic intercostals. A wide variation in the effect of high obstruction of the aorta is explained by extreme differences in the segmental pattern of spinal cord supply. The authors note that in spite of hypothermia or shunt protection of the cord during thoracic aortic surgery, spinal damage is a potential danger when the lower intercostals are permanently ligated.

In spite of this danger, Chamberlain *et al.* (70) have resected what amounts to almost the entire descending thoracic aorta in a patient who had four aneurysms of the thoracic aorta. They used an external shunt of pig aorta to by-pass the area during the resection. The patient did not suffer neurologic damage. Aneurysms of the lower thoracic upper abdominal aorta, involving the celiac, superior mesenteric, and renal arteries, were reported by DeBakey. The original report (71) records the successful operation in four cases with one death due to renal failure, and a later mention brings the figure up to 14 operations with technical success. The procedure devised by DeBakey for this lesion and its successful use was a major stride in arterial surgery. Storey (72) records the usual clinical history of traumatic aneurysms of the thoracic aorta noting that such an aneurysm forms when the adventitia of the otherwise badly damaged artery remains intact. He and his co-workers resected one traumatic aneurysm, replacing it with a graft, evidently encountering very unusual technical difficulties in a 24-hr. operation during which 32 pints of blood were used.

DeBakey (73), Swann & Brarsher (74), and Warren *et al.* (75) report on the use of an operation devised by DeBakey for dissecting aneurysm of the aorta. This procedure, which consists of providing an artificial re-entry for the dissecting lumen, was devised to stimulate the natural process by which some dissecting aneurysms become stable and apparently innocuous

for long periods of time. Swann in his report modifies DeBakey's transection method of doing this and substitutes a longitudinal incision in the thoracic aorta through which the artificial window is produced and the distal dissection is stabilized by suture. Thompson & Austin (76), Nemir (77), and Spencer (78) report on resections of aneurysms of the carotid artery. In Thompson's series of six such aneurysms, four relatively small ones were treated simply by wrapping with fascia or cellophane and thereby became asymptomatic. One operation in which the aneurysm was resected and substituted for by a graft was followed by death without evidence of occlusion of the graft or of cerebral ischemia. Twenty-one minutes of occlusion of the right common carotid artery were required for Nemir's resection and reanastomosis. This period of occlusion produced paralysis of the left arm and leg which lasted for 3-½ hr. after surgery followed by full recovery. The aneurysm resected by Spencer was a very large one, extensively clotted, but after excision it was found that only a 2 cm. segment of common carotid artery was involved to form a large aneurysm. Reanastomosis without a graft was possible. This luetic aneurysm had not been diagnosed previous to surgery because of the failure of the heavily clotted lesion to pulsate.

Examination of the Abdominal Aorta by Aortography

The necessity for aortographic study of the abdominal aorta has been subjected to serious re-evaluation because of reports indicating a potential serious hazard to its use. Possible types of damage include severe general reactions to the injection of the contrast medium, spinal cord damage, traumatic dissection of the aorta, thrombosis or traumatic damage to the mesenteric vessels, and, probably most serious of all, kidney damage because of the injection material. Since all of these injuries are of tremendous gravity, their occurrence even in a very small percentage is disturbing in the performance of a diagnostic procedure.

The occurrence of some of these hazards has been reported during the past year. Gaylis & Laws (79) encountered two cases in which all or part of the injection medium was injected into the medial coat of the aorta producing a bizarre pattern. In animal experimentation they showed that this pattern was characteristic of the accident. Tarazi *et al.* (80) investigated experimentally the possibility of spinal cord lesions in dogs, making the injections with the animal in the supine position. This position influenced the occurrence of spinal cord damage very unfavorably. The authors, however, point out anatomical differences between the blood supply of the cord in dog and that in man which are protective to man. An instance of acute pancreatitis following translumbar aortography is described by Robinson (81). In this patient an initial injection of 20 cc. of 70 per cent iodopyracet (Diodrast) was visualized in the celiac axis, and a second attempt was made showing that the aorta was blocked. It was evident that the first injection was maximally injected into one aortic branch going largely to the pancreas, because 48 hr. after the procedure the patient had

abdominal pain and a marked increase in his previously only slightly elevated blood sugar. He was operated upon three months later at which time fat necrosis was found, and in spite of a successful resection of the aorta the patient died two days after surgery. The autopsy showed extensive hemorrhagic pancreatitis. The toxicity to the kidney of the media specifically used for aortography is well recognized. Thompson, Margolis & Grimson (82) studied the effects on the kidney of injection of various iodine contrast media when these were injected directly into the renal artery. The early and late effect on the organ of four media, each in two concentrations, is reported. The toxicity was not found to be entirely dependent on the iodine content, inasmuch as the medium containing the least percentage of iodine was one of the most damaging. An immediate and unrelieved renal failure following the translumbar injection of 70 per cent sodium acetrizoate (Urokon) is reported by Conger *et al.* (83) who noted that the nephrogram resulting from the injection persisted unusually long and that tubular excretion never did occur. Goodwin (84) made an editorial defense of the use of the aortogram, stressing the use of a small amount of the contrast medium and the generous use of intraarterial novocaine.

Surgery of the Infrarenal Aorta, Iliac and Femoral Arteries

Numerous experimental studies and clinical trials indicate in a general way that most of the available grafting materials and the techniques of thromboendarterectomy will provide a very high percentage of successes in treatment of occlusive lesions of the abdominal aorta and aneurysms of the abdominal aorta in skilled hands. Such a satisfactory situation does not obtain in replacement therapy or thromboendarterectomy in the femoral-popliteal region, and much effort is being expended to develop the most satisfactory graft material for this region. Most experimental testing has been done in the dog using 5 to 7 cm.-length segments of the thoracic or abdominal aorta as the test implantation site. It has been repeatedly suggested that a more reliable site for testing would involve the use of a longer segment of the trial substance requiring implantation as a by-pass from the high thoracic to the low abdominal region of the dog.

Autogenous tissue has received attention because antigenicity would be lacking. Fisher *et al.* (85) constructed tubes of autogenous skin in dogs. Kehne & Sensenig (86) implanted rectus fascia as arterial patches and as tubed grafts. Zech *et al.* (87) studied pericardial tubes implanted in the thoracic aortas of pigs with the purpose of studying the effect of growth. The results of these investigations into nonvascular autogenous tissue were uniform. The skin grafts remained patent in 35 per cent of the implantations but were distorted by irregular stretching. The rectus fascia grafts formed aneurysms in all instances in which they remained patent, and the pericardial tubes in pigs, even though some were supported with addition of fascia, showed aneurysm in all but one instance. It is evident that other tissues than arteries, even though they are supporting tissues, contain

collagen either in a lesser concentration or an inefficient distribution to prevent expansion when this tissue serves as a conduit for arterial blood flow.

Moore *et al.* (88) compared alcohol preservation with a freeze-dried process of homografts for replacement of small arteries. The homografts were implanted in 5 cm. segments in the carotid and femoral arteries in dogs. The technique of placement included the use of an anastomosis made in a double layer with an inner everting mattress suture and an over-and-over suture in the edge. Anticoagulants were not used. Of 111 replacements 61, or 55 per cent remained open, the carotid being slightly more successful than the femoral implants, and the alcohol-preserved grafts being at least as good as the freeze-dried grafts. The effect of heparin was studied in regard to possible impairment in the strength of healing of anastomoses by Bacigalupo *et al.* (89) in 21 animals in which heparin therapy was started at various times, before, during, and after implantation. No demonstrable diminution in strength was seen at various times following the implantation. Kroboth *et al.* (90) encountered failure of a graft to heal in a clinical patient who was on cortisone and he was therefore prompted to study the effect of cortisone on the healing of aortic homografts. Forty-six dogs were used and homografts were implanted from the renal level down to the trifurcation. The strength of the anastomoses was tested seven and fourteen days after implantation. There was no difference in the strength of the anastomoses at these two periods between the cortisone-treated animals and untreated controls. However, a greater incidence and severity of thrombosis was noticed in the cortisone-treated animals.

There is much conjecture as to the nature of the new intimal lining of arterial grafts of various types. Edwards, Rich, & Peter (91) investigated the efficiency of this lining in the prevention of thrombosis in aortic homografts and crimped nylon grafts in the aortas of dogs. A control series of animals was processed along with the experimental series. In each, a 3 cm. segment of the abdominal aorta was clamped above and below in a filled state for a period of 1½ hr. The presence or absence of thrombosis within the excluded segment was determined in experiments that were done after progressively longer periods since implantation of the grafts. There was some indication in the results that the resistance to clotting improves with time. The clinical importance of this observation would be that stasis produced by crossing the legs or lying in the cramped position should be avoided by patients until the end of the unknown period required for the development of the new intimal lining.

The entire principle of arterial replacement for occlusive lesions has been criticized occasionally on the basis that reconstruction of the normal channel abolishes the collaterals which have slowly developed during the progressive obstruction, and that with obstruction of the new channel, the blood supply of the part would be worse than before. Jacobson & McAllister (92) made aortographic studies on dogs before and after re-establishment of arterial flow through the previously occluded abdominal

aorta. In the six complete experiments, the re-establishment of flow caused the previously well-developed collateral circulation to become very markedly reduced.

Heterogenous arterial tissue has been further investigated by Rosenberg *et al.* (93). The physical properties of bovine arteries partially digested in two processes have been studied. In one process the digestion left behind essentially pure collagen tubes. The second process resulted in tubes consisting principally of elastic fibers. The tensile and breaking strength was determined very accurately on special equipment and showed that collagen is highly resistant to stress, while the elastic tissue, though extensible and retractable, is relatively weak. The article refers to continued satisfaction with the implantation of heterogenous tubes prepared by the collagen method implanted in animals. The antigenic properties have been demonstrated to be markedly reduced by removal of other protein. Wesolowski & Sauvage (94) implanted heterologous aortic grafts in dogs in an experiment devised to study the effect of the recipient site and the effect of ethylene oxide freeze-dry preparation on the host reaction. They implanted fresh porcine and ethylene oxide freeze-dried porcine grafts in the thoracic and abdominal aorta of dogs and freeze-dried and ethylene oxide freeze-dried human arteries in the thoracic aorta of dogs. All such heterogenous grafts showed much lytic change which rarely resulted in stenosis, but showed sporadic aneurysm formation. The site of implantation made no difference, and the ethylene oxide treatment of the graft did not protect the heterograft from changes. Kittle & Taquechel (95) implanted dermal heterografts, chamois, as a prosthetic vascular material. They used it as a right ventricle patch, a thoracic aortic patch, a thoracic aortic tube, and abdominal aortic tube, and showed by aortography that there was no appreciable thrombosis.

Mortensen & Grindlay (96) implanted molded seamless tubes of formalinized polyvinyl sponge in the aortas of 17 dogs. These were followed 11 months without showing thrombosis, rupture, or dilatation. Contrary results were obtained by Harrison (97) who used the same material but prepared his tubes by wrapping 3 mm. slices of the frozen sponge on rods and subsequently compressing them by fixation at boiling temperature. Five to 6 cm. lengths of this type of Ivalon sponge tube were implanted in the thoracic and abdominal aorta in 17 animals and resulted in the formation of aneurysm in nine. Harrison states that the Ivalon is somewhat unstable and is water soluble and concludes it is unsatisfactory as a blood vessel. The difference in preparation of the tubes in these two studies may be significant.

Prostheses of steel mesh were implanted as short tubes in the abdominal aorta of 10 dogs by Lary, Meine & De Takats (98). Eight of the dogs survived, and three were found to be occluded 9 to 11 months later.

The clinical use of autologous vein grafts in the peripheral arteries was studied clinically by Lord & Stone (99) and by the reviewers (100). The clinical cases of Lord indicate that in all instances of trauma, peripheral

aneurysms, arteriovenous fistulae, and malignancy the vein grafts remain open, while in nine arteriosclerotic obstructions in which vein grafts were used, four remained patent after a follow-up period less than five months. This dependency of the usefulness of vein grafts upon the patency of the circulation above and below the point of implantation is shared by all methods of vascular replacement. Haimovici & Escher (101) correlated the clinical, x-ray, and intraarterial pressures in 13 patients and concluded that a reduction of 70 per cent in lumen diameter or 82 per cent in area of lumen was necessary for the production of perceptible hemodynamic changes in the circulation through a diseased vessel. By use of the plethysmographic method of Burch, Creech *et al.* (102) followed the changes in digital blood flow after reconstruction of the arterial system by graft in nine cases. These patients, who were between the ages of 60 and 80, showed that there was a delay in the improvement of digital blood flow following successful reconstruction rather than an immediate spectacular increase corresponding to the return of pulses.

One hundred and sixty-nine cases of major arterial grafting were detailed by Humphries *et al.* (103). Humphries had an initial failure rate of 14 per cent, a late failure rate of 3 per cent, a mortality of 11 per cent, and continued success in 169 cases of 72 per cent. Hoye & Warren (104) reported an over-all result of iliofemoral arterial reconstruction which was much less optimistic. Twenty-nine operations in this area in which reconstruction was carried out showed a failure in only three at the time the patients were discharged from the hospital. However, with passage of seven months, nine of 16 homograft artery grafts were closed while eight of 13 vein grafts were closed in nine months. In this series, the grafts 20 cm. or longer closed twice as often as did the shorter ones. In comparison to his results with grafts, Warren (105) later reported 19 patients upon whom thromboendarterectomy of the femoral artery had been done. In these patients there were no deaths. Three of the operations were not completed because of technical difficulties, and four of those completed closed within 24 hr. The remaining 12 early successes remained open except for two which underwent late closure at two months and six months.

The recovery of arterial homografts which had been in a patient for a considerable period of time reported by Creech *et al.* (106) showed that all the grafts seemed to have become adapted to their new location and use, and that they were not replaced by scar tissue. These grafts, which were recovered from patients who died from causes other than a catastrophe in the graft, had been in place 14, 24, 28, and 30 months.

Clinical experiences with the prostheses were made by Ayers (107), Julian *et al.* (108), Edwards & Tapp (109, 110), and a review of vascular prostheses by a committee of the Society for Vascular Surgery selected instances of prosthetic use and analysed them (111). Reports by individuals and groups bear out the committee conclusion that large aortic replacements are almost uniformly successful in a structural sense, while the deficiency

in the clinical application of vascular prostheses lies in the replacement of small vessels such as the femoral.

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DISEASES OF THE KIDNEY (MEDICAL)[1,2]

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The Cushny Memorial Lectures, delivered by ten distinguished British investigators, have been published under the editorship of F. R. Winton (1). A monograph on *Etiologic Factors in Renal Lithiasis* was edited by A. J. Butt (2). Several symposia concerning the kidney appeared during the past year: Symposium on Water and Electrolytes, *Metabolism; Clinical and Experimental,* July, 1956; Symposium on Nutrition and the Kidney, *American Journal of Clinical Nutrition,* Sept.-October, 1956; Essays in Metabolism in memory of Dr. John P. Peters, *Yale Journal of Biology and Medicine,* December, 1956; Symposium on Physiology and Pathology of the Kidney, *British Medical Bulletin,* January, 1957; and Symposium on Glomerulonephritis, *Journal of Chronic Diseases,* January, 1957. A number of the individual papers of these symposia are cited in later sections. McCrory & Macaulay (3) have written an excellent and detailed review of the current methods of treatment of renal diseases in children. The natural history of pyelonephritis was the subject of a review by Keefer (4).

Structure and ultrastructure.—Electron microscopy of the normal glomerulus was described in man, dog, rabbit, and rat by Hall (5, 6), and in the dog by Mueller *et al.* (7). Whether the dense basement membrane is finely porous remains in doubt. Farquhar *et al.* (8) applied electron microscopy to biopsy material obtained from 40 children. In acute glomerulonephritis marked endothelial proliferation and swelling occurred; epithelial proliferation and swelling were also seen, but the foot processes were usually normal. Material resembling basement membrane accumulated in the subacute and chronic stages. In nephrosis, a loss of organization of the epithelial foot processes was seen regardless of clinical phase or extent of pathology seen by light microscopy. Endothelium and basement membrane were normal early; the basement-thickened with increased severity or chronicity. The clinical picture of "mixed nephrosis-nephritis" showed a "mixed" picture of glomerular changes. Early in lupus nephritis the main

[1] The survey of literature pertaining to this review was concluded in July, 1957, and, with some exceptions, covers only the previous year. The following major topics have been excluded because of limitation of space: malformations, neoplasms and infections of the kidney and urinary tract; nephrosclerosis and hypertension; necrotizing nephroses due to toxic agents; nephrolithiasis; diuretics.

[2] The following abbreviations are used in this review: C_{CR} (endogenous creatinine clearance); C_{IN} (inulin clearance); C_{PAH} (*p*-aminohippurate clearance); DI (diabetes insipidus); ECF (extracellular fluid); GFR (glomerular filtration rate); RBF (renal blood flow); RPF (renal plasma flow); SLE (systemic lupus erythematosus).

changes were basement membrane thickening and endothelial proliferation. In the final stages of all three diseases no differences among them were discernible. To increase safety and certainty of success in human renal biopsy, Löfgren & Snellman (9) recommended guiding the needle by a finger inserted in a small skin incision and a bluntly dissected opening through the muscles. Use of intravenous contrast medium and amplified fluoroscopy for biopsy was recommended by Lusted *et al.* (10). An outstanding description of pathology in all stages of epidemic hemorrhagic fever was published by Oliver & MacDowell (11).

Glomerulonephritis.—Several aspects of acute and chronic glomerulonephritis were subjects of excellent reviews: microbiology and prophylaxis [Rammelkamp (12); Schmidt & Rammelkamp (13)]; immunology [Fischel (14)]; renal circulatory changes [Goormaghtigh (15)]; pathology [Ehrich (16)]; natural history [Earle & Seegal (17)]; diagnosis as aided by biopsy [Schreiner (18); Pollak *et al.* (19)]; pathophysiology [Farber (20)]; conservative treatment [Danowski & Mateer (21); Talbot *et al.* (22)]; and treatment by external dialysis [Merrill (23)]. In a clinicopathologic study, based on biopsies in 38 adult patients, Brod & Benesova (24) found greater glomerular damage than suggested by the 24-hr. endogenous C_{CR} if the latter was 30 to 100 ml./min. With C_{CR} over 100 ml./min., most glomeruli were intact; if under 30 ml./min., the majority were out of action. If any three of five quantitative tests (proteinuria, hematuria, leucocyturia, cylindruria, or erythrocyte sedimentation rate) were very abnormal, a highly active disease process was probably present; if four of five, this was almost certain. Combinations of rauwolfia drugs and ganglion-blocking agents are often helpful in treating hypertension due to renal diseases [Abrahams & Wilson (25); Daeschner *et al.* (26)]. Alwall *et al.* (27) summarized their experiences in treating 26 severe cases with the artificial kidney.

Nephrosis.—Reviews were written by Barnett & Eder (28), Merrill (29) and Squire *et al.* (30). The Proceedings of the Annual Conference on the Nephrotic Syndrome, available now at most medical libraries, has become widely recognized as an excellent source of current information. Nephrosis in four children of one family was reported by Vernier *et al.* (31). The clinical spectrum included transient "pure" nephrosis, persistent "pure" nephrosis, mixed nephrosis-nephritis, and chronic glomerulonephritis; pathologic diagnosis from biopsies ranged from "normal kidney" through advanced glomerulonephritis. No differences between these familial cases and sporadic nephrosis could be found; it was concluded that the four cases represented a single etiology and pathogenesis. Two of three cases of nephrotic syndrome with onset at or soon after birth were siblings whose parents were first cousins; 12 additional published cases of congenital nephrosis were reviewed [Giles *et al.* (32)].

The etiology and pathogenesis of human nephrosis remain obscure but progress continues in the field of nephrotoxic serum nephritis and nephrosis in animals [Seegal & Bevans (33)]. Nephrotoxic antigen is not limited to

kidney, but its location in the kidney exposes it directly to injected circulating nephrotoxic antibodies [Baxter & Goodman (34)]. Ortega & Mellors (35) demonstrated that injected antirat kidney antibodies localize almost exclusively in the glomerular tufts and remain there up to three months. From the sixth day to three months after such injection, autogenous antibodies also are found in the tufts in a pattern corresponding to that of the injected antibodies; Kay's postulated mechanism seems fulfilled by these observations. However, immediate massive proteinuria occurring without complement fixation in some animals given nephrotoxic serum suggested a direct combination of kidney antigens with injected antibodies [Stavitsky *et al.* (36); Moench & Rother (37)]. Canine nephrotoxic disease was described by Reich *et al.* (38), Stickler *et al.* (39), and Heymann (40). A new method of producing experimental nephrosis in rats involves injections of an aminonucleoside [Frenk *et al.* (41)]. The pathogenesis of lipide nephrosis and glomerulonephritis is the subject of a spirited review by Ehrich (16). These are distinct pathogenetic entities in his opinion. Extensive endothelial proliferation in glomerulonephritis may be associated with heavy proteinuria and therefore with a clinical picture of nephrotic syndrome; lipide nephrosis is characterized by swelling of the basement membrane. In both diseases, intra- or extracapillary thrombosis may occur and lead to formation of glomerular scars, adhesions, and crescents. The juxtamedullary glomeruli are strikingly more susceptible to obliterative sclerosis in lipide nephrosis than are other glomeruli [Rich (42)]. The natural history of nephrosis was described in 32 children by Todd (43) and in 40 adults by Roscoe (44). An interesting variant is the polycyclic nephrotic syndrome in which proteinuria completely disappears during successive remissions [Rytand & Cox (45)].

Hardwicke & Squire (46) and Malmendier *et al.* (47) acutely elevated plasma albumin concentration in nephrotic patients by large albumin infusions and observed that excretion and plasma concentration of albumin were linearly related. However, the line extrapolated through the concentration abscissa to the right of zero (i.e., albumin clearance increased with increasing plasma albumin concentration) indicating, in their opinion, a "threshold" and a reabsorptive "Tm" for albumin analogous to those for glucose. This belief was based on the implicit assumption that glomerular permeability to albumin remained constant during the period of observation. Such an assumption seems unwarranted because large changes in plasma volume, which probably alter glomerular permeability, result from albumin infusions [Chinard *et al.* (48), confirmed in tables published by Hardwicke & Squire (46)]. Therefore, the validity of the values for albumin "threshold" and "Tm" calculated by both groups (46, 47), as well as the changes in these values resulting from steroid therapy (47), must remain in doubt. All three groups do agree that glomerular permeability to proteins is probably increased in nephrosis. Freeman & Joekes (49) disagree and believe that proteinuria is entirely due to failure of tubular reabsorption of normally

filtered proteins. This conclusion was mainly based on the insufficient evidence that electrophoretic patterns in edema fluid and urine of nephrotic patients showed similar percentages of albumin which were much higher than that of serum (65 to 82 per cent compared to 18 to 49 per cent). Rowe (50) found that the composition of *in vitro* ultrafiltrates of nephrotic serum resembled that of typical nephrotic urine, indicating that selective ultrafiltration alone could account for the protein composition of nephrotic urine. Whether the tubules in human nephrosis absorb more or less protein per minute than in normal subjects remains unsettled. Oliver (51) believes that protein droplets appear in the tubules when the physiological reabsorptive mechanism has been saturated. This depends on the amount and nature of the proteins reabsorbed and whether the mechanism is injured or not. The rate of synthesis of plasma proteins was found to be increased in experimental nephrosis [Drabkin & Marsh (52)]. Hypercholesteremia and hyperlipemia failed to develop in rats following injection of nephrotoxic antibodies if external loss of urine was prevented by ureteral ligation or ureteral-caval anastomosis [Rosenman *et al.* (53)]. The concentrations of cholesterol and total lipides were elevated only in the plasma of nephrotic rats; visceral levels were normal [Rosenman *et al.* (54) and Marsh & Drabkin (55)]. Furthermore, biosynthesis of cholesterol and fatty acids from labelled acetate by liver slices from nephrotic rats was greatly decreased (55). Singer (56) made an interesting observation concerning the possible role of aldosterone hypersecretion in the pathogenesis of nephrotic edema; in nephrotic rats, the adrenal venous blood contained higher concentrations of aldosterone than did that of control rats.

Present steroid treatment of nephrosis consists of administration of Prednisone (delta-cortisone), Prednisolone or hydrocortisone on three consecutive days each week (or daily) for a varying number of months [McCrory & Macaulay (3); Barnett & Eder (28); Lange *et al.* (57). Vallery-Radot *et al.* (58), Friederiszick & Hoffecker (59), and Arneil (60)]. The extensive experience of Mateer *et al.* (61) and Danowski *et al.* (62) with 28-day courses of ACTH has been reported in detail. The importance of recognizing infections during steroid therapy is again emphasized by a report of two deaths from unrecognized cellulitis in adult nephrotic patients treated with Prednisone [Ross & Ross (63)].

Proteinuria.—Lambert *et al.* (64) discussed the possible role of diffusion in the transglomerular passage of proteins. Equal increases of individual protein clearances, relative to GFR, resulted whenever RPF was reduced as a result of epinephrine or *l*-norepinephrine infusion in proteinuric patients [Lathem (65)]. King (66) found that proteinuria in patients with renal diseases increased upon standing only if initial proteinuria was less than 1 mg./min. Reinhardt *et al.* (67) found that atropine, acetazolamide (Diamox), and metabolic alkalosis reduced orthostatic proteinuria. Cloudy swelling in rat tubules, as judged from electron microscopic observations, is the consequence of mitochondrial modification into hyaline granules and

other "degenerative" forms [Gansler & Rouiller (68)]. Sellers (69) suggested that the normal daily glomerular filtration and tubular reabsorption (with breakdown to amino acids in the tubule cells) of plasma albumin accounts for a large fraction of the daily total body turnover of albumin. Independently, Hughes has confirmed this suggestion (70).

Kidney diseases as part of systemic diseases.—Muehrcke *et al.* (71, 72) have made a thorough investigation of the natural history of the nephritis associated with systemic lupus erythematosus (SLE), based on serial biopsies and correlations with simple laboratory tests. Amyloidosis, possibly as a result of steroid therapy, may complicate SLE [Wegelius (73)]. Renal pathology in SLE was studied in aspiration biopsy specimens from 11 patients by Joske & Stubbe (74). The kidney in scleroderma is the subject of reports by Calvert & Owen (75) and Carpent (76). Although some patients did not develop hypertension or renal failure, their kidneys nevertheless showed arteriolar sclerosis; this is against the theory that malignant nephro-angiosclerosis is a result of hypertension (76). Renal involvement in periarteritis nodosa was reported by Bäckman (77) and Suchenwirth (78). Muirhead *et al.* (79) prefer the term "cellular hyaline lesion" for the nodules in diabetic glomerulosclerosis and "acellular hyaline lesion" for the crescentic, globular, oval, or elongated lesions; the cellular lesion stains like collagen, while the acellular lesion is histochemically similar to the hyaline in hyaline arteriosclerosis. Sommers & Haley (80) found a mucopolysaccharide-like material in glomeruli and arterioles of nondiabetics treated with cortisone which had ultraviolet absorptive qualities indistinguishable from those of the nodules of diabetic glomerulosclerosis. Bucht *et al.* (81) measured discrete renal functions in 10 patients with diabetes mellitus, retinopathy, and hypertension; C_{CR} was not a reliable estimate of C_{IN}, and Tm_{PAH} was reduced in proportion to C_{IN}. Freedman (82) described two unusual cases in which death resulted from Kimmelstiel-Wilson type of glomerular damage in patients whose blood and urine sugar values had always been found to be normal. One had hyalinization of the islets of Langerhans and the other partial destruction of the pituitary; both were thought to have had inapparent diabetes mellitus.

The kidney in hematologic disorders.—Defective renal concentrating mechanisms were demonstrated in sickle cell anemia by Heinemann & Cheung (83) and Keitel *et al.* (84). Multiple blood transfusions restored concentrating ability to normal in four infants, slowly and incompletely in a 10-year-old child, and had no effect in two young adults (84); they conclude the renal impairment is secondary to the presence of the abnormal hemoglobins. Kidneys removed for unilateral hematuria in 21 cases of sickle cell disease showed only severe congestion, focal hemorrhages, necrosis, repair and regeneration; nephrectomy should be avoided in young Negroes if other causes of hematuria can be ruled out [Mostofi *et al.* (85)]. Urinary abnormalities are uncommon in children with leukemia, yet at autopsy the kidneys are usually enlarged by leukemic infiltration, with marked paren-

chymal distortion, focal necrosis, and hemorrhage [Gilbert *et al.* (86)]. In patients with primary or secondary polycythemia, GFR and Tm_{PAH} were normal or slightly reduced, RPF was considerably decreased, but because of the high hematocrit RBF was increased [Doering & Wenker (87) and Malizia (88)]. In congenital cardiacs the measurements returned to normal after surgery alleviated the polycythemia (88). Data consistent with these were obtained by Becker *et al.* in normal inhabitant of the Andes living at 15,000 feet altitude (89) and in dogs made polycythemic by chronic exposure to low oxygen tension (90).

Uremia, acute and chronic.—Treatment of emergencies in acute and chronic renal failure was discussed by Farber (91). Epstein (92) described causes of reversible renal impairment occurring in chronic uremia, correction of which makes an important difference to the patient. Principles of dietary treatment were reviewed for acute [Lowe & Valtin (93)] and chronic renal failure [Merrill (94)]. Acute renal failure resulting from intravenous pyelography in 11 patients with 7 deaths was reported by Alwall *et al.* (95). That translumbar aortography is potentially a hazardous procedure was indicated by four new case reports including one death [Berg (96); Conger *et al.* (97); Roy (98); and Dormandy *et al.* (99)]. One way to avoid some of the hazards was described by Edholm & Seldinger (100). A specially designed catheter is passed into either renal artery via a needle in the femoral artery; much smaller doses of contrast medium can now be given. Sevitt (101, 102) observed acute uremia without oliguria in some severely burned patients; all died and were found to have diffuse distal tubular necrosis. Necrosis of proximal tubules was found mainly in elderly burned patients while distal tubular necrosis affected mainly children and younger adults. The role of ischemia in acute renal failure in dogs was reported by Moyer *et al.* (103). When the aorta was clamped above the renal arteries for as long as three hours, no serious renal damage resulted. The renal arterial pressures averaged 30 mm. Hg or less during the clamping, yet this was enough to maintain sufficient renal circulation. A technic in which blood is heparinized on the way from the patient's artery to the artificial kidney and neutralized by protamine on the way back to the patient was developed by Gordon *et al.* (104) to permit dialysis of patients with bleeding tendencies. Kolff & Watschinger (105) developed a cheap, disposable dialyzing unit. Extensive experiences in the treatment of acute uremia with the artificial kidney were reported [Alwall *et al.* (106); Anthonisen *et al.* (107); Palmer *et al.* (108); and Hamburger & Richet (109)]. In acute uremia, Hamburger & Richet (109) invariably found decreased calcium and chloride and increased magnesium and sulfate in the plasma; the disturbances were efficiently corrected by dialysis. Magnesium retention seemed to be responsible for clouding of consciousness and prolongation of the Q-T interval in the EKG (109). Contrary to many earlier impressions, renal function does not return to normal in many patients recovering from acute renal failure. In a majority of 16 patients, Finken-

staedt & Merrill (110) found that discrete renal clearances remained permanently below the lower limit of normal.

Lewis *et al.* (111) found that the bleeding tendency in uremia was associated with platelet abnormalities in 11 of 12 cases, while Kuhlbäck (112) concluded that increased capillary fragility was the major cause. Survival in chronic uremia averaged three to six months after plasma creatinine had risen from below 11 to about 15 mg./100 ml.; as long as the concentration remained below 11 mg./100 ml., a survival of several years was possible [Effersøe (113)]. Prognosis in chronic renal failure seems somewhat better today than 25 years [Effersøe (114)].

Specific tubular defects.—Brief reviews of this complex and still poorly understood group of kidney diseases were contributed by Findley (115) and Stickler & Hayles (116). Richet (117) reviewed renal tubular acidosis, congenital and acquired, and rationalized the use of the artificial kidney in selected cases. Additional case reports of congenital tubular acidosis have appeared [MacDonald (118); Foss *et al.* (119); Monnet & Matray (120); and Kyle & Canary (121)]. Reubi reviewed renal glycosuria (122). Glucose titrations were reported in two cases [Steigerwald & Görlitz (123)]. A high incidence of renal glycosuria occurs in pregnant diabetic women [Perkoff & Tyler (124)]. Renal aminoaciduria was reviewed by Harris (125), and results of nephron microdissection in these syndromes were described by Darmady & Stranack (126). In cystinuria, the clearances of cystine, lysine, arginine, and ornithine were nearly equal to GFR, suggesting that they normally share a common reabsorptive path [Harris & Robson (127) and Robson & Rose (128)]. The multiplicity of renal defects in Wilson's disease have been described [Bearn (129) and Bearn & Gutman (130)]; all are probably due to renal accumulation of copper. Wallis & Engle (131) have carefully reviewed the 18 recorded cases of Fanconi syndrome in the adult. Additional cases of nephrogenic diabetes insipidus (DI) were reported [Linneweh *et al.* (132); Ellborg & Forssman (133); and Kirman *et al.* (134)]. Mothers and other female relatives from four affected families had a decreased ability to concentrate urine [Carter & Simpkiss (135)]. A case of autosomally inherited DI susceptible to vasopressin therapy with mental retardation was described by Ellborg *et al.* (136); having now been observed in two genetically different forms of DI, mental retardation is probably not a part of the genetic pattern but rather the result of dehydration. The syndrome of potassium depletion nephropathy was described by Relman & Schwartz (137) who believe it to be relatively common. Vasopressin-resistant hyposthenuria was the outstanding defect which can be easily measured, but C_{IN}, C_{CR} and C_{PAH} were also significantly reduced. Reviews of this condition were presented by Milne *et al.* (138) and Conn (139). The artificial kidney was used to produce and study hypokalemia in dogs [Young & Daugherty (140)]; plasma concentration fell rapidly to about 1.6 m.eq./l., where it remained despite continued loss of potassium; all EKG changes were correlated with plasma concentration except depres-

sion of ST segment which was more closely related to total quantity removed. In one case of salt-losing pyelonephritis, GFR was constant at 5 ml./min. despite marked changes in plasma NPN and sodium concentrations; sodium excretion remained fixed at about 60 per cent of that filtered [Cleempoel & Karhausen (141)]. In another case, the urinary concentrations of sodium, potassium, chloride, phosphate, and total solutes remained within narrow ranges even when daily urine volume ranged from 500 to 6300 ml. [Knowles *et al.* (142)].

Renal alterations in endocrine and metabolic disorders.—Scholz *et al.* (143) found renal arteriolar sclerosis and renal calculi or nephrocalcinosis in a majority of cases of Cushing's syndrome. In a case of gigantism, acromegaly, and insulin-resistant diabetes, Gershberg *et al.* (144) found greatly increased GFR and Tm for glucose, sulfate, and PAH during life and markedly enlarged glomeruli and proximal tubules at autopsy. Three patients with primary aldosteronism were extensively studied before and after removal of the adrenal tumor [Dustan *et al.* (145)]; specific renal function recovered to varying degrees. Thompson & Hiatt (146) found that phosphate Tm was normal in three hypoparathyroid patients and below normal in one hyperparathyroid patient. Repeated injections of parathyroid extract resulted in decreased phosphate Tm, hypercalcemia, and hypophosphatemia in normal and hypoparathyroid subjects [Hiatt & Thompson (147)]. Results of repeated infusions of buffered phosphate suggested that the parathyroid glands respond to increased phosphate intake by increased secretion of hormone [Thompson & Hiatt (148)]. The relationships of calcium metabolism to the kidney were reviewed by Kushner (149) and Stanbury (150). A case of masked hyperparathyroidism, confused at first with milk-alkali syndrome, was reported by Atlas *et al.* (151).

Renal function in hypothermia.—In 11 human subjects, GFR and RPF averaged 72 and 67 per cent of control when body temperature fell to the range of 29.4 to 32.2°C. [Moyer *et al.* (152)]. In 8 patients whose temperature was lowered to 27 to 32°C. under thiopental plus spinal anesthesia, GFR, RPF, and Tm_{PAH} decreased to 48, 44, and 35 per cent of control, respectively [Morales *et al.* (153)].

Renal function in paraplegia.—Impairment of GFR and RPF was found in about half of 62 cases of paraplegia in spite of modern antibiotic therapy [Morales *et al.* (154)]. Vesicoureteral reflux was present in 10 per cent, bladder calculi in 29 per cent, and pyelonephritis in about 50 per cent. Continuous prophylactic use of antibiotics was urged.

Kidney function tests.—Of 500 patients with asymptomatic microhematuria, 44 per cent had normal urologic findings; no criteria were found for deciding which patients could be spared extensive investigation [Greene *et al.* (155)]. Sargent & Johnson (156) defined the normal alterations in urinary sediment, concentrating function and C_{CR} resulting from changes in diet and activity. In hypertensive patients who benefited from subsequent unilateral nephrectomy, the rate of flow and concentration of sodium were

lower in urine from the diseased than from the normal kidney; in six patients not relieved by unilateral nephrectomy these differences had not existed [Connor *et al.* (157)]. Maximum urinary concentration in response to vasopressin during a water load was greater on high than on low protein diets, and it was greater after three days of dehydration than after three days of hyperhydration [Epstein *et al.* (158, 159)]. The difference in maximum specific gravity of urine resulting from fluid deprivation and vasopressin was small enough to warrant clinical use of vasopressin instead of dehydration [De Wardener (160)]. In patients with hypertension, diabetes mellitus, or rheumatic heart disease, urinary concentrating function was often impaired when other routine tests of kidney function were normal [Frank *et al.* (161)]. After recovery from acute fevers, 30 per cent of patients had a temporary depression of concentrating ability [Bock & Krecke (162)]. The radioactive diodrast renogram is a new external method for testing individual kidney function and upper urinary tract patency [Winter *et al.* (163, 164)]

Renal transplantation.—A major scientific breakthrough was achieved when Merrill *et al.* (165) succeeded in transplanting a kidney from a healthy human donor into his uremic identical twin. Two additional transplants between identical twins have since been successful [Merrill (166)]. A recent review expresses a hopeful attitude concerning problems of homografting [Ferrebee & Merrill (167)]. A variety of parallel clearance studies were carried out after transplantation in the first patient and in the donor twin [Bricker *et al.* (168)]. The transplanted and therefore denervated kidney performed normally, except during acute changes in extracellular fluid volume (ECF) when sodium excretion differed from the normal pattern; it is possible therefore that renal nerves are needed in a normal volume control system.

Regulation of water and electrolyte excretion.—Volume factors were emphasized in reviews by Grossman (169), Wrong (170), and Epstein (171). Acid-base regulation was reviewed by Orloff (172), Roberts *et al.* (173), Seldin *et al.* (174) and Lambert (175). Two reviews concerning water excretion in health and disease were written by Welt (176, 177). Hollander *et al.* (178) found a graded curvilinear relationship between the rates of vasopressin infusion (0.4 to 15.5 milliunits/hr.) and of water reabsorption during maximal water diuresis in normal men. Maximum urine flow in normal men during maintained water load increased after cortisone or hydrocortisone [Raisz *et al.* (179)]. Cortisone intensified polyuria in two patients with diabetes insipidus [Hoel (180); Joseph & Levin (181)].

Many studies of adrenocortical regulation of body fluids involve measurements of hormone excretions in the urine from which rates of secretion of the hormone into the blood are inferred. An important contribution concerning the question of how the human kidneys handle some steroid hormones is that of Daughaday (182), who showed that the renal clearance

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of 17-OH corticosteroids was only 5 to 9 per cent of endogenous C_{CR} and was not altered by probenecid; extensive binding to plasma albumin (94 per cent) was considered responsible for the low clearances. The clearance of the corresponding glucuronides, however, was far greater, averaging 93 to 99 per cent of C_{CR}, with reduction to 55 per cent by probenecid; because the glucuronides were also considerably bound to plasma albumin (65 per cent), it was suggested that tubular secretion may be involved in their excretion. Luetscher (183) and Bartter (184) reviewed the physiology of aldosterone. The most potent mineralocorticoid is the synthetic 2-methyl-9α-fluorohydrocortisone [Liddle *et al.* (185)]. Adrenal nerves probably play no role in secretion of hydrocortisone or aldosterone [Fleming & Farrell (186)], but a hormone from the diencephalon may regulate aldosterone secretion [Rauschkolb & Farrell (187)]. Sodium depletion did not lead to increased aldosterone excretion in dogs unless potassium was provided in the diet [Laragh & Stoerk (188)]. In normal men, potassium depletion by itself reduced aldosterone excretion below control; sodium depletion concurrent with potassium depletion increased aldosterone output to two to six times the control value; potassium repletion during maintenance of sodium depletion caused a further rise in aldosterone excretion [Johnson *et al.* (189)]. In normal men, aldosterone excretion increased after a potassium load, administration of carbonic anhydrase inhibitor, a combination of both, or profuse sweating; from these data Falbriard *et al.* (190) concluded that loss of sodium, excess of potassium or reduction of ECF volume might all be stimuli. Decreases in aldosterone excretion were produced by measures which increased ECF volume even though intracellular water content or serum sodium concentration increased, decreased or remained unchanged [Bartter *et al.* (191)]. Expansion of ECF volume by vasopressin administration resulted in decreased excretion of aldosterone [Muller *et al.* (192)]. Inverse correlations between sodium excretion and aldosterone excretion were reported in normal and edematous subjects by Duncan *et al.* (193) and Buchborn *et al.* (194); the slope of the correlation was different for various diseases. In normal pregnant women and patients with epidemic hepatitis, the ratio of aldosterone to sodium excretion was very large (194). The weight of evidence indicates that aldosterone secretion is largely independent of ACTH control [Liddle *et al.* (195) and Venning *et al.* (196)]; however Muller *et al.* (197) believe that ACTH control exists but that its effect is often masked by other homeostatic mechanisms. Amphenone appeared to inhibit synthesis or release of aldosterone in a majority of normal subjects and patients with a variety of diseases [Renold *et al.* (198)].

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DISEASES OF THE KIDNEY (SURGICAL)[1]

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During the last few years there have been many additions to our knowledge concerning the diagnosis and treatment of renal disorders which are within the province of the urological surgeon. The following review is an attempt to bring together experimental work, diagnostic aids and additions or changes in surgical practice which, in the mind of the author, have contributed to the better surgical treatment of kidney lesions. It is to be regretted that, because of the mass of material, the reporting cannot be complete.

Diagnostic Procedures

Aspiration needle biopsy of the kidney.—In 1951, Iversen & Brun (1) described a method of needle aspiration biopsy of the kidney. Since then considerable interest has developed, in this country and abroad, in this procedure which frequently provides exact histopathological information with very little risk. Recent articles on renal percutaneous needle biopsy are by Muehrcke, Kark & Pirani (2) and by Schweibinger & Hodges (3). The procedure is carried out in order to obtain information relative to the type or stage of renal parenchymatous disease, glomerulonephritis, pyelonephritis, multiple myeloma, amyloid disease, or acute anuria. By serial study with this method, information relative to the course and prognosis of renal disease may be gained. It may guide treatment in the sense that in both acute and chronic renal disease, the knowledge so obtained indicates the patients' probable response to treatment, which may be time-consuming and expensive.

Biopsy should certainly not be done routinely or as a primary means of arriving at the diagnosis of renal disease. It should be used for investigative purposes or to clarify diagnosis after thorough studies including examination and culture of the urine, renal function studies, biochemical blood analyses, cystoscopy and pyelograms, and tests for the efficiency of blood coagulating mechanisms have been made. Hemorrhagic diathesis is certainly a contraindication as is probable or suspected tuberculosis, perirenal abscess, cortical renal abscess, or tumor. Because of the possibility of perforation of a large renal vessel and severe perirenal or intrapelvic hemorrhage there should always be blood available for transfusion. Parrish & Howe (4) report a case in which it was necessary to explore the renal area to control bleeding.

There are two methods of performing aspiration biopsy, either of which seems satisfactory. The technique of Muehrcke *et al.* utilizes the prone

[1] The survey of the literature pertaining to this review was concluded in August, 1957.

position. These authors insist that the patient be hospitalized. Position and size of the kidney are determined by intravenous urograms taken in the prone position. The patient is placed prone with a sandbag under the abdomen. The exact position of the kidney is determined by introducing a fine needle, the location of the needle in the kidney being evident when the portion outside the skin swings through a wide arc on deep inspiration. Biopsy is then done with the Franklin modification of the Vim-Silverman needle. Biopsy specimens were obtained 172 times in 179 attempts. No patient had serious hemorrhage although transient microscopic hematuria was noted in most patients.

Schwiebinger & Hodges recommend intravenous or retrograde pyelograms to localize the kidneys accurately and to rule out malposition or absence. Biopsy is done with the patient sitting erect and the legs over the edge of the bed. They use the Turkel liver biopsy needle of 11 gauge, 100 mm. long with an adjustable guard control, and an inner trephine needle and stylet, 13 gauge, 150 mm. in length. A 20 cc. syringe is used for aspiration of tissue. As a guide to placing the needle they state that

> we measure the relationship of the inferior pole of the kidney to the vertebrae and to the twelfth rib. The right kidney is preferred because of its lower position and the presence of the spleen on the left. Biopsy of the left kidney has been done, however, without incident. In the average individual six finger breadths are measured from the mid line and two fingers breadths inferior to the twelfth rib at that point. This avoids the intercostal artery.

The tissue obtained is described as usually adequate for diagnosis. The ability to obtain satisfactory specimens is, as one would expect, a function of experience. There are many situations in urology in which exact information obtained by biopsy would be helpful. It would seem that in each large hospital at least one man should be trained to carry out needle biopsy of the kidney.

Aortography and retroperitoneal pneumography.—The techniques for aortography, both by percutaneous lumbar and femoral artery puncture, have been in use long enough so that any comments on technique are superfluous. Comments on the use of aortography seem warranted.

The newer contrast media, 70 per cent sodium acetrizoate (Urokon Sodium) and 50 per cent sodium diatrizoate (Hypaque), give equally good visualization but the latter appears to be less toxic than any agent to date. Good visualization of the renal arteries is obtained with the use of only 10 cc. of the medium. The procedure is associated with a slight risk due to the possibility of direct injury to vessels or indirect effect of the contrast medium on the parenchyma of the kidneys or other organs, notably the spinal cord. This risk is probably considerably less when sodium diatrizoate is used in small amounts. Paraplegia has followed aortography at times (5, 6). The pathogenesis of this is not entirely clear. Arterial shunts that direct the contrast medium directly into the spinal circulation seem the most likely cause.

Because of the risks, at least until more experience is gained, it would seem best to utilize the procedure when it alone may provide information on which diagnosis and treatment may be based. Its use to differentiate renal cyst from tumor seems superfluous since experience has shown that findings are often not conclusive or to be depended upon (7). In most clinics it is felt that regardless of the probable diagnosis, space-occupying lesions of the kidney require exploration, assuming that age and condition of the patient warrant treatment.

Aortography used to demonstrate the circulation of an adrenal tumor may be worthwhile, since preoperative localization of an adrenal tumor may make the choice of incision and thereby the surgical exposure and extirpation easier. It seems likely, however, because of confusing upper abdominal vascular patterns, that most adrenal lesions may be as well or better delineated by retroperitoneal pneumography. This may be done by introducing through the flank, a needle, the point of which perforates Gerota's fascia, or by presacral injection as advocated by Rivas (8) in 1950. Combined aortography and retroperitoneal pneumography (9) provide the ultimate in diagnostic study for adrenal, renal, and other retroperitoneal tumors but this combination is not likely to be often used.

A word about the risks of retroperitoneal pneumography is in order. Ransom, Landes & McClelland (10) encountered a fatality from air embolism in the course of performing this procedure and subsequently gathered information concerning the risks involved. Questionnaires were sent to 1736 urologists. The survey of 1267 replies revealed that retroperitoneal pneumography is a frequently used diagnostic procedure. Six hundred sixty-eight of the 1267 urologists performed presacral pneumography. Three hundred twenty-one of these had performed 9201 presacral pneumographies. One hundred seventy-five urologists performed retroperitoneal pneumography by the flank route. One hundred four of them indicated the number they had performed to be 2221. Fifty-eight deaths from gas embolism were revealed by this survey. Twenty-four followed the presacral procedure with 34 following injection through the flank. Sixty-four severe, nonfatal cases of gas embolism were collected. Thirty-three followed the presacral procedure and 31 the flank procedure. This seems to corroborate the general impression that the presacral route is safer. Of those who reported the gases used, 78 were using oxygen, while carbon dioxide and helium each had two advocates. Twenty-five of the 34 deaths in the flank group were injected with air and two with oxygen. Gases used in the remaining seven were not mentioned. Eleven of the 24 patients in the presacral group who died were injected with air, five with oxygen, and one with helium. The number of deaths and nonfatal reactions resulting from oxygen were not proportionally less than those caused by air. Although only two urologists reported using carbon dioxide, irrefutable evidence shows that it is the safest gas to use. Moore & Braselton (11) injected carbon dioxide directly into the pulmonary vein of dogs. Under direct vision they saw the bubbles course into the left atrium, thence into the left ventricle and aorta. They saw

the gas enter the coronary arteries and disappear into solution without producing any untoward reaction. When air was used death resulted. Recently, carbon dioxide has been purposely injected by catheter technique in relatively huge amounts to fill the cardiac chambers as a contrast medium for cardioroentgenography. It enters solution so rapidly that no embolism occurs. These authors suggest, therefore, that carbon dioxide be used for retroperitoneal pneumography. It would seem that there can be no controversy concerning this point and that retroperitoneal pneumography can be safely done.

Aortography has its greatest usefulness in the study of the renal arterial circulation. No other study can provide specific information, as will be shown later, on which the diagnosis of hypertension due to renal arterial disease can be made. In this connection, Poutasse (12) has shown that satisfactory renal angiograms are often difficult to obtain in the presence of hypertension because the injected material is diverted from the orifices of the renal arteries into the central aortic stream. Temporary reduction of blood pressure with vasodepressor drugs makes it possible to obtain better renal angiograms with only 10 cc. of injected contrast material—50 per cent sodium diatrizoate.

Vena cavagram.—An addition to the usual urological diagnostic methods, abdominal venography, has been described by Kaufman, Burke & Goodwin (13). These investigators performed vena cavagrams on 50 patients by bilateral femoral vein puncture, percutaneous femoral vein catheterization and translumbar cava puncture. Caval phlebography has been used to demonstrate invasion or compression of the inferior vena cava by renal and metastatic testicular neoplasms, and to aid, in conjunction with retrograde pyeloureterograms, the diagnosis of retrocaval ureter. Since radical surgery for renal tumors occasionally necessitates the removal of a segment of cava or extraction of a tumor thrombus, preoperative knowledge of involvement will aid in planning surgery.

New renal function test.—Winter (14) has described a renal function test—the radioactive Diodrast renogram. This is performed, following the intravenous injection of I^{131}-labelled Diodrast, 1 mc./3 kg. of body weight, by externally measuring with gamma ray scintillation counters, over each kidney region the rate of accumulation and disappearance of radioactive material in the two kidney areas. Each kidney area has been tested for 30 min. periods. The results from studying 216 patients, some with normal renal function and others with a variety of renal lesions, vascular lesions, tubular dysfunctions, and obstructive uropathies have led to the recognition of normal and abnormal curves of renal radioactivity. The reader is referred to the original article for details which may not be included here. Winter suggests that the test may provide a tool for fruitful basic renal physiologic research as well as possibly providing a differential renal screening test for use in large clinics, hospitals, employment centers, and the armed forces where large numbers of individuals have to be examined.

It would seem to this author that if findings are substantiated and the test capable of useful elaboration it may become valuable in spite of initial cost of equipment. It is conceivable that it might be useful for screening hypertensive patients for the possible presence of vascular renal disease which is at the moment becoming important.

Cineradiography and cinefluorography.—One of the most exciting additions to urological diagnosis is provided by electron intensification of an x-ray image. It has become possible by the use of apparatus already available to study and photograph with the cinecamera the details of renal pelvic and ureteral emptying (15, 16). When this method becomes more practical and generally available it would seem that the diagnosis and treatment of pelvic and ureteral as well as bladder abnormalities which are now poorly understood will be greatly simplified. The chief advantage will be the small amount of radiation necessary to provide good visualization as well as allowing adequate periods of observation.

Surgical and Experimental Advances

Hypertension.—Since Goldblatt demonstrated that partial occlusion of one or both renal arteries in dogs was followed by hypertension there has been a considerable effort by urologists to cure hypertension by the removal of one kidney suspected of being the site of disease responsible for hypertension. Smith (17) states that

> from 1937 (when Butler (18) published the first report of the relief of hypertension by nephrectomy) to 1956 there have been performed 575 nephrectomies on hypertensive patients with demonstrated or suspected unilateral impairment of renal function. Of this number, the blood pressure has been reduced to 140/90 or below, for one year or longer, in 26 per cent. This record is accepted as demonstrating that unilateral renal disease, amenable to surgical correction, can cause either benign or accelerated hypertensive disease in man.

The pathogenesis (Smith) in 149 patients in whom unilateral nephrectomy has apparently been successful in curing hypertension is as follows: Pyelonephritis, 62; pyonephrosis, 4; atrophic kidney, 18; hydronephrosis, 23; tuberculosis, 6; ureteral occlusion, 2; perirenal hematoma, 2; renal cyst, 2; renal tumor, 5; radiation sclerosis, 1; infarct, 3; thromboangitis obliterans, 1; intrarenal vascular sclerosis, 1; aneurysm of renal artery, 4; arterial occlusions of all sorts, 10; 4 causes were not known.

Criteria for diagnosis in general have been the demonstration in a hypertensive individual of urological disease which in itself required nephrectomy. For a long time there has been need for other dependable criteria on which diagnosis might be based. Howard (19) observed a 37-year-old man with right-sided abdominal pain, microscopic hematuria and pyuria who, 4 months later, developed severe hypertension with retinal exudates and hemorrhages. Intravenous urograms were normal. Simultaneous collection of urine from each kidney yielded less urine from the right kidney than

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Criteria for diagnosis in general have been the demonstration in a hypertensive individual of urological disease which in itself required nephrectomy. For a long time there has been need for other dependable criteria on which diagnosis might be based. Howard (19) observed a 37-year-old man with right-sided abdominal pain, microscopic hematuria and pyuria who, 4 months later, developed severe hypertension with retinal exudates and hemorrhages. Intravenous urograms were normal. Simultaneous collection of urine from each kidney yielded less urine from the right kidney than

the left and sodium concentration in the urine from this kidney was lower. Aortography disclosed constriction of the right main renal artery. After right nephrectomy the blood pressure fell rapidly. At the time of the report the patient had been normotensive for 9 months. Pathologic study of the kidney showed no renal lesion. Because of these findings and similar findings in other cases Howard has felt that the demonstration of diminished urine excretion, sodium excretion and urine osmolarity by one kidney as contrasted with its mate, in the presence of otherwise normal function tests and normal intravenous urograms might provide useful criteria for the diagnosis of hypertension due to unilateral renal artery disease. There is evidence of support for his findings but it would seem that aortography or renal angiography provides the information needed in disease of the renal arteries.

The most important contributions to this field have been made by Poutasse *et al.* (20, 21). In the first article Poutasse reported two cases with rapidly developing hypertension. Translumbar aortography demonstrated in one case no filling of the arterial circulation to the lower pole of one kidney and in the other case no visualization of the main renal artery of one kidney. Nephrectomy was carried out in both cases with relief of hypertension. Pathological diagnosis in one case was old, partial occlusion of the lower secondary branch of the main renal artery due to fibrosis. Renal atrophy was noted distal to the occlusion. Pathological diagnosis in the second case was occlusion of the main renal artery by a thrombus. There was focal tubular atrophy and arteriosclerosis of intrarenal arteries.

In the second paper stenosis of the first portion of both renal arteries was demonstrated by translumbar aortography in a 15-year-old boy in whom the development of hypertension had been observed over a period of five months. Average blood pressure was 200/120 mm. Hg. Intravenous urograms showed prompt and satisfactory function of both kidneys and no significant structural change in either. The aortogram showed dilatation of the left renal artery just distal to the narrowed segment. Urine collected from both kidneys demonstrated satisfactory concentrating powers by each. The diagnosis of renal hypertension was made on the basis of stenosis of both renal arteries and operation was planned to correct the situation.

At the first operation, the left kidney was approached by a subcostal incision. The left renal artery, just distal to the aorta, was found to be narrowed to less than half the diameter of the more distal artery. A pronounced thrill was palpable. The kidney was soft but had a normal appearance. A special angled arterial clamp to permit incision of the aortic wall without obstructing aortic blood flow was applied to the aortic wall just below the narrowed renal artery. A lyophilized femoral artery homograft was sutured end-to-side to an incision in the aorta. The narrowed segment of the renal artery was then ligated and excised. The homograft was sutured end-to-end to the normal distal portion of the renal artery close to the hilus. The kidney was deprived of arterial circulation for only 5 min. When

blood began to flow through the homograft the kidney immediately returned to normal color and became firmer than it had been previously. Recovery from operation was uneventful. Five days after operation an intravenous urogram showed both kidneys functioning normally. Two weeks later the right kidney was operated through a mid-line incision and the renal artery stenosis was resected and replaced by a graft. Translumbar aortography subsequently demonstrated that both arterial homografts functioned normally. No evidence of constriction was visible. During the second week after the second operation the average blood pressure was 130/76 mm. Hg. Pathological study of sections of arteries removed showed obstruction of their lumens by fibrous proliferation of the intima.

The diagnostic and therapeutic problems illustrated so well by these cases opens a new field for possible treatment of hypertension. In addition to the lesions of the kidney demonstrated by cystoscopic study and intravenous urography which may occasionally be causally related to hypertension, renal arterial disease must be searched for. Aortography or more limited renal angiography provides the only dependable diagnostic tool. A complete study in an effort to find the cause of hypertension must include this procedure.

Renal artery aneurysm.—Another paper by Poutasse (22) is well worth reading on the subject of renal artery aneurysms. He found reports in the literature of 129 renal artery aneurysms and added 12 of his own. He classified renal artery aneurysms into saccular, poststenotic or jet aneurysms, fusiform, false, and arteriovenous. Seven of the 12 patients had saccular aneurysms. Only two of these had symptoms—intermittent upper abdominal pain. Three had poststenotic lesions with hypertension, one had a fusiform aneurysm in association with a large renal tumor, and the last had an arteriovenous aneurysm which followed nephrectomy. The most consistent roentgen evidence of saccular aneurysm is found to be a calcified, ring-like shadow near the hilum of the kidney. The others, because of lack of calcification, could only be demonstrated by aortography. Poutasse found that three authors have reported successful resection of small renal arteries containing aneurysms with preservation of the kidneys but only one report of excision of the aneurysm and repair of the arterial wall (23). Treatment of his seven cases with saccular aneurysm was nephrectomy in four; excision of the aneurysm and repair of the artery in two patients involved careful dissection of the artery to demonstrate the origin of the aneurysm. After the application of an arterial clamp to the proximal renal artery, the aneurysmal wall was excised by cutting its neck where there was no palpable evidence of calcified arteriosclerosis. After removal of the aneurysm the defect in the artery was closed by a simple running arterial suture. There were no complications. Postoperative intravenous urograms showed normal renal function.

Renal artery aneurysms may rupture and cause death but, in most instances, rupture has occurred in the presence of noncalcified aneurysms. It

is suggested by Poutasse that surgical treatment is unnecessary in nonhypertensive patients having small, calcified aneurysms.

Other interesting possibilities for conservative renal surgery are suggested by a case reported by Ellis *et al.* (24) in which there was found an aneurysm of the abdominal aorta involving the renal artery supplying an ectopic right kidney. An aortic graft was inserted after the aneurysm was excised. The renal artery was anastomosed to the stump of the coeliac axis of the graft. Postoperative intravenous urogram and aortogram showed normal renal function on both sides and a patent graft. It is obvious as one reads these reports that a team of interested medical men, surgeons, and urologists will be necessary for the diagnosis and treatment of such cases.

In connection with this work on renal arterial disease and aneurysms a paper by Creech *et al.* (25) is of interest. These authors discuss the length of time during which the renal blood supply may be safely interrupted. In dogs it was demonstrated that the aorta could be occluded for 2 hr. above the renal vessels with depression of the glomerular filtration rate and renal blood flow to 90 per cent of normal three days later. When the left renal artery was occluded for 2 hr. the glomerular filtration rate and renal blood flow were diminished to 50 per cent of normal three days later. When the aorta above both renal arteries and the left renal artery were occluded studies revealed severe diminution in left renal function but normal renal function on the right. These observations suggest to the authors that renal function is preserved under these conditions by collateral vessels which are not operating if occlusion of both the aorta and renal artery occurs simultaneously. The clinical application of this is cited in four cases in which resection of large abdominal aneurysms involving both renal arteries was accomplished. In one case, following occlusion of both renal arteries for 1 hr. and 45 min., the patient died from renal insufficiency. In the other three cases, a temporary shunt was constructed from above the occluded aorta to the lower aorta below the aneurysm. Using this technique it was possible to resect the aneurysms with occlusions of the renal arteries for less than 1 hr. Subsequent renal clearances and blood flow studies indicated only temporary diminution. Renal function returned to normal. The importance of having subfiltration arterial pressure in the distal aorta is thought to be of great importance.

Renal transplantation.—The problems incident to auto- and homotransplantation of the kidney have been investigated at length by Dempster in England and by the group at the Peter Bent Brigham Hospital in Boston. The results of this to date indicate that because of immunological and genetic differences which cannot as yet be overcome by all attempts to modify the antibody response, rejection of the homograft occurs. In dogs, homografted kidneys have been rejected in 3 to 15 days. In the human the homograft kidney survives longer and in one instance adequate renal function persisted for 5½ months (26). On the other hand, autotransplanted kidneys in dogs have successfully survived. Murray *et al.* (27) have utilized the

iliac vessels for anastomoses and have placed the transplanted kidney retroperitoneally in the pelvis which allowed implantation of the ureter directly into the bladder. This, they feel, places the kidney in its normal thermal environment and obviates many of the difficulties inherent in transplantation to the neck and thigh. The authors have shown that a renal autotransplant performed in this way, totally denervated and revascularized, survived indefinitely without detectable impairment of function. The opposite kidney was removed and subsequent careful studies, up to 2½ years, revealed the autotransplanted kidney to be completely normal when renal function tests were applied. Postmortem examination revealed the transplanted kidney to be 60 per cent larger. Microscopic examination of the glomerular tufts and tubules revealed no abnormality. Vascular anastomoses and ureterovesical anastomosis showed minimal reaction.

Since skin homografts between identical twins have survived permanently it was reasoned that renal homotransplantation between identical twins might also be successful. Merrill and his associates carried out such a procedure. This promises to be a classic paper and should be consulted in the original (*26*). Briefly, the details are as follows: A 24-year-old white male twin whose illness began with edema and hypertension became uremic and was found to have suffered extreme atrophy of both kidneys. Preparation included the accumulation of evidence that the patient and his brother were monozygotic twins. Final decision to carry out transplantation of a kidney from the healthy twin to the patient rested on the best evidence—survival of transplanted skin between the two. Transplantation was carried out using the technique utilized in animals. Total anoxia of the transplanted kidney was 1½ hr. Postoperative study showed that the transplanted kidney functioned well. Subsequently, the paitent's own contracted kidneys were removed and one year later hypertension had disappeared.

Since the first transplant three other twins have undergone successful renal transplantation (*28*). The author has been told that at the time of the last renal transplantation the kidney which was removed for transplantation was supplied by three renal arteries. Here is another instance in which preoperative aortography may be of extreme importance. Continuing studies in the field of antigen-antibody relationships may some day make possible homotransplantation of kidneys between persons other than identical twins.

Hydronephrosis

It has been assumed that, when hydronephrosis develops because of an obstruction of a ureter or ureteropelvic junction, renal secretion continues by virtue of transmission of urine in some fashion from the renal pelvis back into the circulation. Persky, Storaasli & Austen (*29*) have given us information regarding this. They ligated the ureter of dogs close to the ureteropelvic junction around a tube leading to a mercury manometer, instilled radioactive I^{131}, serum albumin labelled with I^{131}, and Au^{198} into the renal pelvis and then measured the blood concentration of the radioactive

materials. In control animals the intrapelvic pressure rose fairly rapidly and usually fell after a peak had been reached at 15 to 20 min. The decline in pressure during the experimental period never reached the initial low level. Both radioactive albumin and radioactive iodine were rapidly absorbed and soon found in the blood. The level of radioactive gold in the blood was less than that of iodine and iodinated albumin. Concentration of radioactivity within the peripheral blood continued to rise when pressure within the renal pelvis fell. This study indicates that the reabsorption of pelvic contents does occur. More important was the demonstration that the reabsorption did not occur when the intrapelvic pressure was normal. Backflow or reabsorption is not a simple diffusion process since molecules of the size of albumin and particles of radioactive gold can be recovered from the peripheral blood. This suggests that backflow or reabsorption results from a mechanism which permits ready access to the blood stream, pyelovenous or pyelotubular backflow, and that at least for the larger particles there must be actual tears in the lining of the pelvic mucosa and adjacent vessels, perhaps a direct shunt.

Further work by Persky (30) utilizing radioautographs of sections of dogs' kidneys, the pelves of which had been exposed to radioactive iodinated albumin under pressure, suggests that reabsorption occurs by way of pyelotubular and pyelointerstitial channels. No direct vascular shunt was demonstrated.

Experimental studies by Goodwin & Kaufman (31) on renal lymphatics show that under conditions of diuresis or ureteral occlusion or both, thoracic duct lymph flow is increased. It is believed by these authors that the source of increased lymph is the kidneys and that some of the fluid is elaborated at pyelolymphatic backflow originating in the interstitial spaces of the kidney.

In this same vein and important from a clinical standpoint, is the question of the effect of total ureteral obstruction on the kidney. In other words, how long may a ureter be totally obstructed with hope of restoration of function after relief of obstruction? Kerr (32) has attempted to answer this question by studying the return of renal function after release of total ureteral obstruction present for 7 to 28 days. As one might expect, kidneys obstructed for one week showed the most improvement in glomerular filtration rate and renal plasma flow; kidneys obstructed for four weeks, the least. The nonobstructed contralateral kidney was removed from five dogs two days after the release of obstruction from the opposite ureter. The removal of the normal kidney resulted in a more prompt and greater increase in glomerular filtration rate and effective renal plasma flow, as well as a prompt increase in the rate of urine flow by the previously obstructed kidney. Removal of the normal kidney in three dogs whose ureters had been obstructed two, three, and four weeks caused an elevation of the nonprotein nitrogen which never returned to normal. The ability of the previously obstructed kidney in all groups to concentrate urine was impaired while

ability to dilute urine and to produce an alkaline and acid urine was not impaired. In three dogs the contralateral or normal kidney was removed a number of days after maximum recovery of the obstructed kidney had occurred. In each case renal clearances increased, demonstrating that even after long periods of stabilization (approximately two years in one dog) the kidneys could still be stimulated to increase the glomerular filtration rate and effective plasma flow.

This substantiates the clinical view that even after a considerable period of ureteral obstruction kidneys are worth saving if the cortex remains reasonably thick. Furthermore, since it is difficult to know the time of ureteral obstruction with any accuracy in many cases and how long complete obstruction has existed, one must adopt a conservative attitude particularly when renal function is badly needed.

Nesbit (33) calls attention to the desirability and even the necessity for performing intravenous pyelograms during pain in the study of patients presenting symptoms of intermittent pain in the upper abdomen or renal areas. This is so because patients who suffer from attacks of pain due to intermittent hydronephrosis may have pyelograms that are entirely normal in the interval between attacks. In such cases the urologist will miss the diagnosis completely if it is assumed that normal pyelograms exclude the diagnosis of intermittent hydronephrosis. Persistent dilatation of the renal pelvis depends on a continuing obstruction such as true stricture, but if the mechanism for the production of hydronephrosis is a fascial band or aberrant vessel which may exert pressure upon the ureteropelvic junction only under unusual circumstances, overhydration, for instance, then the abnormal pyelogram will occur only on such occasions. Five cases are cited to illustrate the point.

Nesbit states

> there are other examples of these transient phenomena. For example, pyelograms made during an episode of ureteral colic will demonstrate either nonvisualization of the renal pelvis or hydronephrosis, yet pyelograms made the next day after the attack may be normal. Delayed cystography has revealed the amazing fact that some children with ureteral reflux may have excretory pyelograms that are entirely normal, yet cystograms made during delayed cystography will reveal enormous dilatation of the ureter and renal pelvis. Thus it is evident that the musculature of the upper urinary tract possesses great resiliency and that pyelograms which appear normal do not necessarily exclude the possibility of intermittent obstructive uropathy.

Hydronephrosis due to ureteral obstruction by retroperitoneal inflammation and fibrosis.—In 1948, Ormond (34) described an interesting, puzzling, previously unrecognized, and still unexplained syndrome of bilateral ureteral compression and obstruction by a retroperitoneal inflammatory reaction. He reported two cases each having complete obstruction of the ureters. Since then at least nine other cases have been reported and it is quite likely that many more have been encountered since the author knows of three unreported cases in the Boston area. The pathological process is a diffuse

granulomatous type of inflammation with fibrosis frequently extending from the kidneys to the sacral promontory and across the retroperitoneum from one ureter to the other. The origin of the inflammatory process is apparently not in the urinary tract. It differs from the local periureteral inflammation and fibrosis described by Vest & Barelare (35) which presumably results from primary urinary tract infection with periureteral lymphatic spread. The origin of the retroperitoneal inflammation is unknown although a case reported by Iozzi & Murphy (36) ultimately was found to have a constricting inflammatory lesion involving the sigmoid suggesting that the diverticulitis may have been the original focus.

The principal features of the cases have been poor general health, back or flank pain, anemia, fever, and varying degrees of upper urinary tract obstruction. There may be sudden anuria, or oliguria, and elevation of the nonprotein nitrogen. In a few patients the disease had been at first unilateral but progressed to involve the opposite ureter. The diagnosis is arrived at by investigation to explain flank pain or anuria and is suggested by finding hydronephrosis of one or both kidneys or nonfunction of one or both by intravenous urography. Cystoscopy and passage of ureteral catheters is apt to be accomplished easily; when retrograde filling of the ureters is attempted dilatation of the renal pelvis is demonstrated, but the ureters fail to fill well because the extrarenal inflammatory process compresses the ureters, pushing the radiographic medium up into the pelvis or into segments of the ureter which are not compressed above or below the obstruction.

Treatment has not been standardized. Temporary nephrostomy, pyelostomy, or ureterostomy has been performed as well as ureterolysis and even transplantation of the ureters intraperitoneally after lysis. In general, after lysis, the upper urinary tract has gradually returned toward normal but not always so. This entity is important to recognize and must be differentiated from carcinoma of the ureter (this was the primary diagnosis in a personal unilateral case), malignant lymphoma, reticulum cell sarcoma, and Hodgkin's disease. If one ureter is involved, there is considerable chance that the other will be later.

Hydronephrosis due to obstruction at the ureteropelvic junction or in the upper ureter.—Causative lesions are congenital strictures, accessory vessels to the lower pole of the kidney, high insertion of the ureter, valves, fascial sheets or bands, external inflammatory fibrosis, nephroptosis, and neuromuscular dysfunction. Combinations are common. Strictures of the ureteropelvic junction may involve considerable segments of the upper ureter. During the last 25 years much effort has been made to develop surgical techniques to correct or eliminate the obstructive factors in the interest of conservation of renal tissue. At the 1956 meeting of the American Urological Association held in Boston, a group of authorities participated in a panel discussion on hydronephrosis (37). The reader is urged to read the discussion which details the indications for the Foley Y plasty, spiral flap operation of Culp, excision of strictured area and reimplantation

of the ureter into the renal pelvis, Davis' method of longitudinal incision without suture and with intubation for long strictures of the ureteropelvic junction and upper ureter.

Results obtained are indicated by Culp's experience in operations on 196 patients at the Mayo Clinic during the last five years. Nephrectomy was performed for 69 patients (35 per cent) because the kidneys were deemed irretrievably damaged. Various plastic procedures were performed in 127. Forty-seven per cent were considered well, 42.8 per cent were considered improved and 10.2 per cent were unimproved. Creevy (38) analyzed his results in 73 patients subjected to the Foley Y plasty. Results were excellent in 60.3 per cent, good in 23.4 per cent, and poor in 1.3 per cent. Fifteen per cent were failures. Various reasons are given for poor results. The point is that there is still room for improved techniques or perhaps better choices of techniques now available.

One of the most amazing reparative processes in the human yet encountered was the demonstration by Davis (39) and Davis, Strong & Drake (40) that, after resection of an elongated segment of part of the circumference of a ureter, regeneration of the wall takes place, including muscularis. This observation forms the basis of the Davis operation of intubated ureterostomy for the treatment of long strictures of the ureter or ureteropelvic junction. Regeneration of the muscularis was questioned for a time but work by Kimbrough *et al.* (41), Lapides & Caffery (42), Boyarsky & Duque (43), and a very ingenious experiment by Hinman & Oppenheimer (44) have substantiated Davis' original observations.

There is much current discussion concerning the desirability of placing splints in the ureter following plastic procedures on the ureteropelvic junction or ureter. This has been more or less standard practice with the thought that splints performed functions of maintaining the ureteral lumen during healing, held the ureter in a straight line to prevent kinking or angulation, and when combined with a nephrostomy or pyelostomy tube provided free drainage of urine. Attention was focused on this matter by the work of Hamm (45) who observed satisfactory healing following plastic procedures on the renal pelvis and ureter without the use of splints or nephrostomy drainage. His method of procedure has been to leave a small opening in the renal pelvis and simply drain the wound with a rubber wick placed to this vent. He and Weinberg further demonstrated that it was not necessary to leave a ureteral splint in place following incision of the ureter for stricture (46). Longitudinal defects in dogs' ureters were created by excising a longitudinal segment comprising one-third to one-half the ureteral circumference in 11 dogs. The ducts were not sutured or intubated. Urine drainage was provided by a rubber Penrose drain. One dog died on the 14th postoperative day. The others were sacrificed 21 to 150 days after surgery. All showed complete regeneration of the mucosa of the ureter. In seven the ureter healed with adequate lumen. An adequate lumen lined by epithelium was noted as early as the 14th day after operation. Replacement or re-

generation of the musculature of the ureter took place after the defect had been filled in with connective tissue. Musculature was thin at first but in animals in which the ureter was allowed a longer period of regeneration normal thickness was noted.

As a result of this work and the desirability of avoiding splints and drainage tubes to avoid the introduction of infection, the trend in plastic surgery on the renal pelvis and ureter is to follow Hamm's lead. A recent report by Webb, Smith & Price (47) of 18 patients with successful plastic operations on the ureter without the use of splinting catheters supports this view.

Renal tuberculosis.—Before the advent of antituberculosis drugs, unilateral renal tuberculosis was considered best treated by nephrectomy and ureterectomy if the ureter was dilated or grossly damaged. Conservative therapy was advocated for bilateral renal tuberculosis although some urologists advocated removal of the worst kidney if it was obstructed or essentially functionless. All this has changed. Antituberculous therapy has been so effective in the treatment of renal tuberculosis that at the Research Unit for Genito-Urinary Tuberculosis, Kingsbridge Veterans Hospital, Bronx, New York, during the preceding three years no kidney or portion of a kidney had been removed for tuberculosis (48). Since the last war, Lattimer and his co-workers have had the opportunity of treating a large number of veterans with renal tuberculosis. Various therapeutic regimens have been used, streptomycin alone, isoniazid alone, streptomycin plus aminosalicylic acid, and the combination of streptomycin, aminosalicylic acid, and isoniazid. The severity of the kidney lesions treated was highly comparable in each group of patients. All had kidney lesions of the moderately or far advanced cavitary type. Patients with minimal renal lesions were not included because these lesions proved to be so easy to arrest that they do not constitute a good test of treatment. The most effective therapeutic combination has proved to be streptomycin, 1 gm. twice weekly, isoniazid, 100 mg. three times a day, and sodium aminosalicylic acid 5 gm. three times a day. Treatment was given continuously for one year. A group of 20 patients had, at the time of publication of the article, completed one year of treatment and one year of follow-up. No relapses of the urine cultures to positive had occurred in this group. Bed rest of a semi-ambulatory type has been considered an important adjunct during the first six to twelve months of treatment. Comparative measures of effectiveness of the regimens were: streptomycin alone given 120 days, 39 per cent negative cultures after two years; isoniazid alone for one year, 60 per cent negative cultures after two years; streptomycin with sodium aminosalicylic acid for one year, 93 per cent negative cultures after two years.

In private practice, at least, it is now relatively rare to encounter renal tuberculosis. In our experience patients with this disease are usually foreign, born in countries where the incidence of active tuberculosis is much greater than in this country.

Renal lithiasis.—Much experimental work is currently in progress in an attempt to elucidate the mechanism or mechanisms responsible for the formation of calculi in the kidney. As yet, however, knowledge is insufficient to allow one to give more than experimental evidence and express opinions.

In the past, stone formation in the kidneys has been considered to be a precipitation of crystals in urine supersaturated in regard to uric acid, cystin, calcium phosphate, calcium oxalate, etc. This concept has been supported by finding increased amounts of these substances in the urine of some but not of all patients with renal calculi. Attempts at prevention of recurrences have been directed toward (*a*) decreasing the amount of these substances excreted in the urine by limiting them or their precursors in the diet, or preventing their absorption from the bowel; (*b*) decreasing their concentration in the urine by increased urine volume excretion; (*c*) increasing their solubility by alterations of the urinary pH, and more recently by using acetylsalicylic acid as a calcium solubilizer (49); (*d*) correcting specific metabolic alterations; (*e*) removal of parathyroid tumors, treating infection and relieving obstructions. There seems to be no question that all of these efforts have been successful to some degree. The presence of colloids in the urine has been known for a long time. It has been considered that these substances take part in the solubilizing of crystalloids by a process of adsorption. We are beginning to realize that these thoughts are superficial to the real problem which is illustrated by the following brief summary of experimental data and personal views.

Boyce, Garvey & Norfleet (50) have isolated the urinary biocolloids (their term for urinary colloids) and found that they consist of at least two mucoproteins. The largest single component was a carbohydrate protein conjugation joined by polymer linkage to form a compound of high molecular weight. They further found that these mucoproteins were greatly increased in the urine of patients with calcium calculi. Two patients with hyperparathyroidism had the highest concentration of any patients studied. The authors suggest (51) that the organic matrix of calculi may be a modified or activated form of the mucoproteins normally found in urine. Boyce's concept of stone formation is that the initial and essential phase is a condensation of mucopolysaccharides and mucoprotein molecules constituting a coagulum of uncalcified matrix which may vary in size from a few molecules to a mass large enough to fill a renal calyx or pelvis. Deposition of inorganic crystals is a secondary phenomenon which usually occurs quite rapidly but may require weeks to reach maximum density in large calculi. The deposition of crystals is governed by the principles of physical chemistry which control the formation of crystals from complex solutions. The origin of calculus matrix remains unknown but the presence of similar or identical mucopolysaccharides in connective tissue and in calculus matrix has been demonstrated. The stone matrix could be derived from bone matrix or connective tissue outside the urinary tract.

Baker & Connelly (52) consider that the high molecular weight of

mucoproteins in the urine makes it unreasonable to assume that their presence in the urine is the result of filtration throughout the glomerulus or of secretion or excretion by the tubule. Experimental work by Baker *et al.* (53, 54) demonstrated alterations in the renal tubule connective tissue mucoprotein immediately preceding the development of calculi in rats. This was observed consistently with four different methods of producing experimental renal calculi. Needle biopsy specimens which were obtained from both kidneys in a small number of patients with unilateral calculi revealed bilateral alterations of the renal tubule connective tissue matrix or mucoprotein. In the rats renal calcification or stone formation occurred in the altered mucoprotein whether within the kidney (nephrocalcinosis) or the renal pelvis or urinary bladder. As a result of these and other observations it is their impression that formation of urinary calculi may not be a disease of urine but rather a systemic condition specifically involving the renal connective tissue matrix of both kidneys. Baker thinks evidence is accumulating that pathological calcification anywhere, including renal calculi, is a disease of connective tissue matrix and as such is essentially a collagen disease.

When the problem of renal calculus disease is considered from this standpoint the following factors are necessary for calcification: (*a*) calcium and phosphorus must be available in the serum and urine, but clinical and experimental evidence has shown that it is not necessary to stone formation that they be present in quantities greater or less than normal, (*b*) an etiological factor is necessary to convert tissue matrix or mucopolysaccharide specifically to a calcium-binding mucoprotein; (*c*) specific contributing factors are needed. These include such conditions as dehydration, prolonged bed rest, infections, increased intake of diary products, hypercalcemia, hypercalciuria, obstructive uropathy. They seem to trigger the basic mechanism in a patient who is already disposed to stone formation. The vast majority of persons with one or more of these contributory factors never develop calculi. The factors result in stone formation only when they are combined with some other specific process as yet not defined.

Baker goes on to say that on the basis of this evidence, altered connective tissue mucoprotein, he has used "anti-inflammatory" drugs in treatment of animals with a known incidence of calculi and in a study of patients with recurrent stone, with reduction of recurrence to nearly 50 per cent. Drugs used were acetylsalicylic acid, cortisone acetate, other corticosteroid hormones, phenylbutazone, and corticotropin. He cites the work of Snapper, Bendien & Polak (55) who showed that sodium salicylate inhibits precipitation of urinary colloids and concludes that this concept of salicylate action is more tenable than the assumption of Prien & Walker that the administration of salicylate increases the solubility of calcium by virtue of increased glucuronide excretion in the urine.

This by no means exhausts the material on stone formation. Consideration is being given to the effect of environmental factors, sex, infections,

the role of citric acid as a calcium solubilizer, and many other interesting factors. It is impossible to project future developments in this important work but it is almost certain that from it will be formulated concepts on which will be based intelligent therapy to prevent recurrence of renal calculi.

There are no recent significant new developments in the field of surgical therapy for calculi. Effort has been made to adapt ultrasonic technique to the disintegration of calculi but up to this time it has not proved practical.

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HEMOSTATIC DISORDERS: HEMOPHILIA AND THE HEMOPHILIOID DISEASES[1,2]

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Hemophilia and hemophilioid diseases are ordinarily understood to be hemorrhagic disorders resulting from alterations in the plasma, determined by inheritance or mutation, which interfere with an effective prothrombin-converting and fibrin-forming mechanism. In limiting this review to these diseases and closely related problems it was necessary to omit detailed consideration of the many hypotheses regarding the coagulation mechanism. Reviewers of this field today are presented with many problems in addition to the rapidly expanding literature. One of the most complex of these problems results from the diversity of laboratory methods, often newly devised and frequently modified. Interpretation of data is dependent upon the detailed understanding of the procedures used. When possible, only the more commonly used procedures have been mentioned. It is not possible in this space to describe each procedure here; however, excellent books pertaining to procedures have appeared recently (1 to 4).

Another problem confronting the reviewer is the matter of nomenclature. Since there are no comprehensive standards for the various clotting factors, names used are based upon their apparent activity in various coagulation systems. This results in several names for each factor, but considerable caution needs to be exercised before assuming synonymity of terms. For example, it was common to assume that patients described as having a deficiency of SPCA, stable factor, Convertin, or Factor VII represented a single deficiency state. Recently, however, it has been shown that certain bleeders in this group have a deficiency of the Stuart factor (5, 6). Mistaken identity of other factors may exist. Nevertheless, in order to give a more concise summation of recent work, only relatively few terms for clotting factors will be used, with probable synonyms indicated.

The subject of this review, while only a segment of the larger field of blood coagulation, has received a great deal of attention in the recent past. The milder forms of hemophilia and the hemophilioid diseases are being recognized with increasing frequency. With better management, the

[1] The survey of literature pertaining to this review was concluded in July, 1957.

[2] The following abbreviations were used in this chapter: AHF (antihemophilic factor); PTC (plasma thromboplastin component); SPCA (serum prothrombin conversion accelerator); PTA (plasma thromboplastin antecedent).

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life span is being increased of those afflicted with the more severe forms. Thus, the magnitude of the "bleeder problem" is gradually increasing. Important as these diseases are in themselves, the real reason for so much attention being given to them is probably more basic. Nature has provided genetically determined derangements in the clotting system, not subject to the artifacts of the laboratory, which, if completely understood, could unravel many of the mysteries of the coagulation and hemostatic mechanism.

Hemophilia and Antihemophilic Factor

Nomenclature.—Hemophilia refers to a recessive sex-linked bleeding diathesis in which the coagulation and hemostatic defect can be corrected by a plasma protein. This protein, antihemophilic factor (AHF), is similar in some properties to fibrinogen and like fibrinogen is not easily absorbed onto $BaSO_4$. AHF has also been called AHG, thromboplastinogen, Factor VIII, and platelet cofactor I (2).

Hemophilia is known variously as true hemophilia, classical hemophilia, and hemophilia A. The term hemophilia vera has been applied to hemophilia by Quick (7), but Lenggenhager has used this term for Christmas disease and parahemophilia and suggested neohemophilia to denote hemophilia (8), since one of the oldest pedigrees of bleeders has proved to be Christmas disease. Mild hemophilia and subhemophilia are used to designate the very mild forms of this disease. Although routine clotting tests may be normal in mild hemophilia, plasma AHF levels are low but measurable with appropriate tests.

Relative incidence and genetics.—Most diagnostic surveys of bleeders indicate that 40 to 90 per cent are hemophiliacs, and that most of the rest have a deficiency of plasma thromboplastin component (PTC), (9, 11, 13, 14, 15, 16, 209). In a study by Graham, the ratio of hemophiliacs to Christmas disease patients was 6 to 1. The frequency of hemophilia in Danish males was calculated at 373 per million (16). About 25 to 50 per cent of cases of hemophilia are reported to be sporadic (13, 17, 18, 19, 209). More careful study of the pedigrees of the probands would probably reduce these figures considerably. About 25 per cent of one series of cases had a normal clotting time (209); the same figure has been given for the incidence of clinically mild cases (18). That these figures represent the actual relative occurrence of the mild forms of hemophilia is doubtful, because of the greater difficulty of laboratory diagnosis of this group, and because many of the group do not seek medical attention for bleeding problems.

Although the sex-linked recessive type of inheritance appears firmly established in hemophilia (16, 20), certain problems in genetics remain. The broad range of normal AHF values reported by Langdell *et al.* (21) has been confirmed (22, 23). The multiple allele hypothesis has been proposed by Brinkhous & Graham (24) to explain the broad range of normal values and the relative constancy of both degree of AHF deficiency in a given pedigree and of severity of symptoms in hemophilia. Verstraete

& Vandenbroucke (223) reported marked differences in the plasma AHF of hemophiliacs in a single pedigree; the accuracy of assays used becomes critical for this point. Graham has reconsidered the multiple allele hypothesis in relation to certain heterozygotes, who have a low AHF level approaching that of subclinical hemophilia, and in relation to females with mild hemophilia (16). He pointed out that modifying genes at other than the hemophilic locus on the X-chromosome may influence the synthesis of AHF.

Hemophilia in the female is still a rarity except in our hemophilic dog colony. A remarkable pedigree has been reported from Czechoslovakia by Pola & Svojitka (25). A cousin marriage of a heterozygote and a hemizygote resulted in three hemophilic siblings, two of whom were females. One of the female bleeders married, having a hemophilic son and a phenotypically unaffected daughter. One other case report of a female hemophilic, without family history, has appeared (26).

Pathophysiology of hemophilia.—In addition to the hypothesis that hemophilia is due to a deficiency of plasma AHF, a number of other hypotheses are current. Two recent studies have supported the hypothesis that hemophilia is caused by excessive inhibitor or an anticephalin that interferes with clotting. Seegers and his associates (12) found that certain coagulants—platelet factor 3, platelet cofactor I, and the combination (threone)—failed to correct completely the prolonged clotting time of the blood of hemophiliacs of various grades. They suggested that the hemophilic blood is antagonistic to these coagulant factors, in keeping with the inhibitor excess hypothesis. In the other study by Carroll, Tocantins, *et al.* (27), normal and thrombocytopenic recipients, transfused with grade IV hemophilic blood, developed a prolonged clotting time which persisted up to 5 days. The possibility of complicating circulating anticoagulant needs to be carefully excluded in the hemophilic donors in experiments of this type.

Restudies have been made of some of the basic experiments on which the inhibitor excess hypothesis was based. Using both human and canine hemophilic blood, Graham & Barrow reproduced the marked shortening of the clotting time of hemophilic blood on dilution, the biphasic curve (28). Evidence is presented which suggests that the biphasic curve is caused by uncontrolled ionic strength rather than resulting from dilution of an inhibitor. It has been reported that prothrombin consumption of hemophilic blood is improved by dilution; neither Verstraete (29) nor Graham & Barrow could confirm this (28). The accelerated clotting of hemophilic plasma following treatment with asbestos, kaolin, or glass was reproduced (28, 29, 30), but plasma treated in this manner had no corrective action when transfused into hemophilic dogs (28). It was suggested that asbestos treatment of plasma caused the elaboration of a $BaSO_4$-adsorbable accelerator, rather than the removal of an inhibitor. Such an accelerator was shown to develop following ether treatment of hemophilic or normal plasma.

With ether treatment of normal plasma, however, there was concomitant inactivation of AHF (28). These findings are in accord with the reports that ether-treated plasma is inactive in the thromboplastin generation test (17, 31), and with Wolf's report that ether-containing AHF fractions lose activity (32).

The question of platelet function in hemophilia has also been restudied, and the close interrelationship between AHF, platelets, and vascular integrity has received increased recognition (33, 34). Axelrod, in a series of tests (35), has confirmed that platelets from normal and hemophilic subjects have the same coagulant activity. On the other hand, Mann (36) observed that little coagulant activity developed in the co-thromboplastin test if washed hemophilic platelets were substituted for washed normal ones. He suggested the possibility of strong adsorption of AHF onto the normal platelets. Fonio has reported that hemophilic platelets maintained their integrity longer and agglutinated less rapidly than normal platelets (37). This may be merely a consequence of the slow clotting of hemophilic blood.

In spite of numerous negative reports it is still frequently suggested that some component of complement is deficient in hemophilia. Normal complement titers in hemophilic and hemophilioid disease sera were found by Sharp (38). Stefanini & Moschides (39) have corroborated the previous reports of Bernfeld and Stefanini that with classical electrophoresis there is an abnormal protein component in hemophilia. With paper electrophoresis of hemophilic serum, Wilkinson, Turner, & Bottomley (40) found an increase in gamma globulins but no abnormal components.

Diagnosis.—Definitive diagnosis of hemophilia depends upon the failure of the patient's $BaSO_4$-treated plasma to correct the coagulation defect of a previously diagnosed patient. This can be a simple qualitative mixing experiment, which is adequate for the characterization of marked deficiencies, or a technically more difficult quantitative assay, which is necessary for the characterization of mild deficiencies. A presumptive diagnosis is possible with the finding of a normal prothrombin time along with a prolonged partial thromboplastin time, abnormal thromboplastin generation test, or impaired prothrombin utilization. The abnormal test results must be corrected by $BaSO_4$-treated normal plasma. The use of serum as a source of AHF-deficient serum factors has become widespread since the finding that serum contains only about one per cent of the plasma AHF activity (41). When used in presumptive diagnostic procedures, serum is apt to be misleading, as there is a synergistic effect of serum accelerator factors and AHF (42).

A wide variety of coagulation tests has been used for the laboratory diagnosis of hemophilia. Langdell has pointed out that many of these, including whole blood clotting time and prothrombin utilization procedures, are sensitive to changes in AHF activity only in the 0 to 2 per cent range (43). The partial thromboplastin test appears to be sensitive to changes

in AHF over a wider range than is the thromboplastin generation test (44). In order to make the thromboplastin generation test sensitive over a wider range, additional dilutions of the test plasma were used by Pitney (18). Some of the difficulties of such a modification have been analyzed by Miale & Garrett (45). The problem of the diagnosis of hemophilia and its differentiation from the hemophilioid diseases is indicated by the number of articles on the subject that have appeared recently (14, 18, 46 to 59).

Management of hemophilia.—Methods of management of hemophilic hemorrhages have been described (60). An interesting panel discussion by Aggeler, Alexander, Rosenthal, Tocantins, and Dameshek has appeared on this subject (61). Hemarthrosis, one of the commonest and most bothersome findings in severe hemophilia, has been thoroughly reviewed, with new data presented on the pathology, diagnosis, and management (62 to 66). The distribution and age of occurrence of hemophilic hemorrhages have been determined in one study by Hartmann & Diamond (13). They found that bleeding occurred in the first 10 days of life in 35 per cent of the patients. Bleeding was umbilical, or intracranial, or operative from circumcision. Hemarthroses occurred in 85 per cent of the patients before they were three years old. Neurological complications have been reported in 7 per cent of the hemophiliacs reviewed by Hartmann & Diamond (13) and Douglas & McAlpine (67). Hemorrhage into the pharynx and larynx is relatively uncommon; Colman has described the successful management of one case without intubation or tracheotomy (68). The recurring problem of distinguishing between acute appendicitis and local hematoma into muscle has been described by Macpherson & Learmont (69). Radiological diagnosis of a hemorrhage into the transverse colon has been reported (70).

Surgical intervention in hemophilia remains a major problem, but better results are being attained because of careful diagnosis followed by adequate replacement therapy (71). Several reports of surgical management have been made, both successful (13, 72) and unsuccessful (73). Local procedures in the management of dental extractions have been outlined (74, 75). The first careful studies of the psychiatric (76) and medicosocial problems (77, 78) of hemophiliacs and their families have been published.

Many procedures and drugs have been advocated from time to time as being curative in hemophilia. The idea of splenectomy was a vogue recently. In a thorough study of the effects of splenectomy on the clotting and hemostatic defect in both human and canine hemophilic subjects, this procedure has been shown to be without beneficial effect (79). Possible benefit by treatment with lysozyme has been reported (80).

Replacement therapy with plasma or plasma fractions.—The need for repeated transfusions at frequent intervals to maintain the hemostatic level of plasma AHF has been well established in the treatment of hemophilic hemorrhages (43, 60). In addition, Brinkhous & Penick have shown that there is more rapid utilization of AHF with tissue necrosis (81), and

Langdell (43) has discussed the need of prompt treatment for potentially serious hemorrhages if a vicious circle of increasing tissue damage and increasing need for AHF is to be avoided. It has been shown previously that plasma AHF levels fall rapidly after transfusions, half of the AHF disappearing from the plasma in a few hours (60). An extension of these studies has been made in hemophilic dogs given potent AHF fractions (82). It was found that if the AHF was maintained at moderate levels in the hemophiliac for many hours, the rate of fall-off was relatively slower. Distribution of AHF between vascular and extravascular compartments could account for the very rapid loss of AHF in hemophilic subjects after single transfusions. Although it is easier to raise AHF levels by intravenous injection, subcutaneous and intramuscular administration of a potent fraction of AHF have been shown to be effective with hemophilic dogs (82).

Work on fractionation of AHF for transfusion is continuing and was recently summarized by Wagner & Thelin (83). The relatively low AHF potency of human plasma and the large volume of plasma required for fractionation have been serious obstacles to the preparation of useful human fractions. The low potency of Fraction I as ordinarily prepared and the difficulties of using this fraction instead of plasma have been shown by several workers (83 to 86). The value of potent human plasma fractions in treatment of hemophilic hemorrhages has been demonstrated by Kekwick & Wolf, who used a fraction precipitated from plasma with cold ether (87).

Assay.—Since all work on the purification and study of AHF is dependent on a specific and sensitive assay of this clotting factor, investigators have given much attention to devising suitable procedures. Hemophilic plasma is used as a substrate in the assays based on prothrombin utilization (88) and on the partial thromboplastin time (89). Another test using a hemophilic substrate has been introduced based on serum prothrombin times (48). These three tests are most likely specific for changes in AHF. Some general procedures for assay of AHF have been used which avoid the need for hemophilic plasma substrate. An artificial hemophilic substrate obtained from the first supernatant in the ether fractionation procedure has also been used for AHF assay (32). Other types of assay are based on thromboplastin generation (23, 90) or on thrombin generation (18, 91). $Al(OH)_3$ is frequently used as the adsorbing agent in the preparation of the AHF-containing control plasma for the assays (23). However, AHF may be adsorbed onto $Al(OH)_3$ (92), and this may be a source of error in the procedure (86). Other problems connected with using the thromboplastin generation test as a quantitative specific test, in contrast to its use as a diagnostic test, have been elaborated by Miale *et al.* in a series of publications (45, 93, 94). Another type of procedure not requiring hemophilic plasma uses purified reagents entirely (95, 96). To insure specificity, materials potent in the test are also checked for their effect on the clotting of hemophilic blood. It has been pointed out by Graham *et al.* (42) and

by Seegers *et al.* (12) that such a procedure may not be specific. It is obvious, from the many procedures described, that AHF assays are beset with many technical difficulties; some of these have been critically evaluated by Soulier (97).

Results of most assay procedures are expressed in per cent activity compared to a standard, or they may be merely in terms of clotting times in the test used (48). Two separate and different units of AHF, both based on the amount of thromboplastin activity developed as reflected in prothrombin conversion, have been proposed (32, 95).

Purification: chemical and physical properties.—Basic methods used for purification have been reviewed (97). The acid precipitation technique has been revised by using adsorbed plasma; a solution 4 to 8 times concentrated has been obtained (86). Modifications of the ethanol-low temperature technique have yielded improved preparations from human (95, 98), bovine (99), and canine plasmas (83, 92). A difficult problem has been the separation of fibrinogen from AHF. A potent fibrinogen-free preparation was described in which fibrinogen was removed from canine plasma by adsorption onto fuller's earth (100). This has also been accomplished by heat precipitation of the fibrinogen (98), by glycine extraction of a bovine Fraction I precipitate (99), and by combined alcohol-ether fractionation (95). Plasma fractionation with ether has yielded a product about 20 times concentrated, suitable for therapy (87). Salting-out procedures have yielded potent animal fractions. Bidwell has done elegant work, salting-out AHF from bovine, porcine, and ovine plasmas with phosphate buffers and sodium citrate (101, 102). In our laboratory, $(NH_4)_2SO_4$ fractions of canine plasma have been about 75 times purified. Porcine plasma, using a modified phosphate-citrate precipitation method, yielded a product about 800 times purified, which is about 4000 to 8000 times as potent as human plasma (83). Kaolin has been used as an adsorbing agent with $(NH_4)_2CO_3$ as the eluting agent by van Creveld and his co-workers (98); the product was so low in protein that the question was raised whether AHF is actually a protein.

Wagner and associates (83, 92) have determined a number of properties of AHF. $Al(OH)_3$ adsorbs both fibrinogen and AHF, predominantly the former. The reverse situation was found with Seitz filtration of canine plasma, giving an artificial hemophilic plasma. AHF is said to be a beta globulin (98), although definitive electrophoretic patterns have been difficult to attain because of protein-protein interactions and irreversible adsorption onto paper (83). Ultracentrifugal studies indicate that AHF sediments more rapidly than fibrinogen, suggesting a high molecular weight if protein interactions can be excluded. Our best AHF preparations have shown a typical protein ultraviolet absorption curve (83).

Heat inactivation of AHF has been confirmed repeatedly. It is more heat stable than fibrinogen (41), but it is almost completely destroyed by

10 min. heating at 56°C. (103). After 3 hr. at 49°C. thermal inactivation of bovine AHF is incomplete and an anomalous denaturation curve is obtained (83).

Attempts to isolate AHF from tissues with different techniques have yielded products active in the thromboplastin generation test, but *in vivo* testing was not done (104, 105). Nour-Eldin & Wilkinson have found normal thromboplastin activity in hemophilic saliva (106).

Stability of AHF on storage.—Older work has indicated that AHF is an extremely labile clotting factor. The work of Penick and his co-workers (60, 103) has indicated that, with proper precautions, AHF is relatively stable in stored plasma, whether liquid, frozen, or lyophilized. Practically all of the activity may remain in liquid or frozen plasma for 3 weeks, and in lyophilized plasma AHF is stable for years. Stabilization of AHF is observed in adsorbed plasma (41, 107). Thrombocytopenic bloods are more stable on storage, and rate of loss of thromboplastic potency parallels disruption of platelets (108). Platelet-free frozen plasma retains its AHF (32). Dilution of plasma increases its storage stability (23). A common denominator in all these studies may be the sensitivity of AHF to relatively small amounts of thrombin, even in the absence of free calcium (107). Small amounts of thrombin may form during collection and storage that may inactivate AHF, even though inadequate to cause clotting. Regardless of the type of anticoagulant used, temperature of storage, and the AHF level of the donor, it was found that the prevention of incipient clotting by careful collection of blood and prompt decalcification was most important for AHF stability.

Increased lability of AHF in oxalate is now well established (103); this may account for the sensitivity of the thromboplastin generation test to even short periods of storage of the adsorbed plasma reagent (45). It has been indicated that storage of blood or plasma in a CO_2 atmosphere, pH 6.1 to 6.5, will stabilize AHF at room temperature (109). A possibly divergent finding was the relative instability of AHF at pH 6.2 to 6.4 when disodium citrate was used as an anticoagulant (108).

Function of AHF in clotting.—Many experiments and hypotheses have been developed regarding the nature of the reactions involved, but it is generally recognized that complete elucidation of the reactions in which AHF participates has not been accomplished. An excellent review of much of this work has been written by Macfarlane (110). It has been confirmed that AHF is consumed in the process of clotting, and that there is impaired consumption in Dicumarol-type plasma, in Christmas disease plasma, and in heparinized plasma (111). Penick has shown that disappearance of AHF appears to be related to and dependent on evolution of trace amounts of thrombin (107).

It has been over a decade since it was clearly demonstrated that platelets and AHF are both needed for the development of thromboplastic activity in plasma and for prothrombin conversion. It has been noted in

the thromboplastin generation test that if serum, adsorbed plasma containing AHF, and calcium are preincubated, a more active coagulant forms (112). The coagulant then forms with platelets a Flynn-Coon type of sedimentable thromboplastic material (113), which Bergsagel & Hougie have called Product I (112). The data of Shafrir, de Vries & Krejnis (114) are in accord with the suggestion of Owren that AHF acts in the formation of convertin (115). From their work with platelet cofactor I and the threone system, Seegers and his associates doubt that a preliminary reaction occurs. They also found that calcium concentration is not critical in their system (116). That AHF is actually a platelet cofactor has been questioned by Wolf on the basis of experiments on prothrombin conversion with varying quantities of AHF and platelets (32). A possible key to the autocatalytic mechanism of clotting may be furnished by the recent work of Penick (107), mentioned above. AHF disappeared in the presence of thrombin alone. AHF disappeared in the presence of cephalin and calcium only if prothrombin was present. Somewhat similar findings have been reported on the role of thrombin in the formation of a fully activated thromboplastin (117).

Sulfhydryl-blocking agents appear not to interfere with either AHF or PTC in the way that they do with prothrombin, thrombin, and autoprothrombin (118, 119). Trypsin appears not to require AHF for its coagulant activity (120). The accelerated clotting time caused by glass contact is independent of AHF, although AHF is needed for full effectiveness of the "accelerator" (30)

Vascular Hemophilia

Nomenclature.—It has been accepted generally that hemophilia is associated with a normal bleeding time. However, certain patients with reduced AHF also have increased capillary fragility and a long bleeding time. This type of hemorrhagic tendency has been called vascular hemophilia (121, 122) or pseudo-hemophilia type B (123).

Pathophysiology of the defect.—Previously reported cases have been reviewed recently by Singer & Ramot (123) and by Soulier & Alagille (124). Several new family studies have been reported by Matter *et al.* (121), and by Schulman and his associates (122). The clinical manifestations are those of a familial hemorrhagic tendency affecting both sexes. Laboratory findings included long bleeding time, increased capillary fragility, normal platelet numbers, and slight prolongation of whole blood clotting time, impaired prothrombin consumption, and defective thromboplastin generation. AHF activity is decreased but only moderately. Matter and his colleagues (121) found AHF activity in their patients to range from 3 to 75 per cent (normal 60 to 190). Singer & Ramot's patient had 19 to 22 per cent AHF activity (123). Platelet morphology was studied by electron microscopy by Matter and associates and was found to be normal (121). Abnormalities in vascular structure of nailbed capillaries and bulbar conjunctivae have been reported (122).

Genetics.—The mode of genetic transmission of vascular hemophilia appears to be different from hemophilia, although AHF levels in both appear to be determined genetically. Matter and associates present evidence that the hereditary pattern is that of an autosomal dominant gene with high penetrance and variable expressivity (121).

Management.—The effect of plasma transfusion on this hemostatic defect is interesting. Schulman and his co-workers found that fresh frozen normal plasma administered to a patient resulted in correction of not only the whole blood clotting time and prothrombin consumption, but also the bleeding time (122). A similar corrective effect with an AHF fraction is reported by Nilsson and associates (125). However, the corrective effect of plasma transfusion on the bleeding time was not seen by Singer & Ramot (123), nor by Alexander & Goldstein (126). The effect of cortisone therapy on the bleeding time was studied by Soulier & Alagille and was found to be ineffective (124).

PTC Deficiency

Nomenclature.—This sex-linked recessive bleeding tendency was first recognized as distinct from hemophilia in 1952 (127, 128, 129). In the first report to appear, Aggeler and associates (127) named the factor that was lacking in their patient's plasma, plasma thromboplastin component (PTC). Several months later Biggs *et al.* (129) reported a similar deficiency which they called Christmas disease after the surname of a patient. Since that time numerous names have been proposed for this hemophilioid state including Hemophilia B and Deuterohemophilia. Numerous presumed synonyms for the deficient factor have appeared. These include Factor IX, autoprothrombin II, and beta thromboplastin (110).

Pathophysiology of the defect.—This disease resembles hemophilia clinically, but in general is considered to be less severe. However, severe hemorrhagic episodes do occur, as indicated by the findings in five cases with neurological complications reported recently by Douglas & McAlpine (67). The coagulation defect is not detectable in the presence of tissue thromboplastin; the prothrombin time is normal. Characteristic findings include a long partial thromboplastin time, poor prothrombin utilization, and impaired thromboplastin generation. The corrective principle is present in normal human serums as well as plasma. Rabbit blood is reported to contain the same amount of this factor as human blood (130).

It is generally believed that the coagulation defect is due to the simple deficiency of a plasma protein. However, Seegers & Johnson have stated that in PTC deficiency, platelet cofactor II is prevented from functioning normally by an inhibitor (131). Freudenberg & Oeri have suggested that platelets may be abnormal in PTC deficiency (132).

Most investigators believe that PTC deficiency represents a distinct entity since diagnosis depends upon the lack of mutual correction of deficient plasmas. However, Sjølin has described two types of PTC deficiency based

on thrombin generation studies (133). This has been clarified by a more recent publication explaining that a patient believed to be PTC deficient, whose defect was not corrected by horse plasma, was found to have Hageman trait (134).

Physical and chemical properties.—The biologic characterization of PTC appears less advanced than that of AHF. This is due at least in part to lack of a satisfactory assay for PTC activity (135). Attempts to quantitate PTC have been made by diluting the serum reagent of the thromboplastin generation test (101, 136). Many proposed assays for PTC are based on the assumption that if serum from a PTC-deficient patient is used as a substrate, the only variable is PTC. It now appears that this is an erroneous assumption since the Stuart factor has been recognized to be present in serum and has been shown to affect thromboplastin generation, prothrombin utilization, and the partial thromboplastin time (5). Deutsch has recently stated that reports of combined PTC and proconvertin deficiencies probably represent a single deficiency of the Stuart factor (17). Haanen may have been studying Stuart factor activity when he suggested that PTC and proconvertin were identical (137). Perhaps more of the properties previously attributed to PTC will be found to belong to Stuart factor.

It has been reported by numerous investigators that acquired deficiencies of prothrombin are accompanied by deficiencies of PTC. Reduction in plasma PTC following Dicumarol or similar anticoagulant therapy has been reported (138 to 144). Lewis and co-workers report the response of PTC to vitamin K_1 oxide to be slower than prothrombin and proconvertin, requiring about 5 days (141). In normal infants, the reduced PTC levels (145, 146) are comparable to those shown for prothrombin nearly two decades ago (147). Variable results are reported on studies of PTC activity in the newborn. Fresh and his associates found PTC activity to be reduced in umbilical cord blood (148), McElfresh *et al.* report thromboplastin generation as abnormal in infants (145), while Barkhan reports the same test to be normal (136). In many cases of acute and chronic liver diseases, PTC is reported to be decreased (139, 140, 141, 149). PTC has been reported depressed in some patients with uremia (141). It should be kept in mind while evaluating these reports on the biologic activity attributed to PTC, that Stuart factor has not been recognized until recently.

Past work on the properties of PTC has been reviewed by Aggeler (135) and Macfarlane (110). The factor is removed from plasma by Seitz filtration and is readily adsorbed from normal human plasma and serum by $BaSO_4$ and similar "prothrombin adsorbants." The factor is relatively stable over a wide pH range (4.2 to 10.1). Although generally considered to be more stable than AHF, it is completely inactivated when heated at 56°C. for 10 min. PTC activity is concentrated in the 45 to 50 per cent $(NH_4)_2SO_4$ fraction of normal human plasma. Aggeler reports that a twenty fold purification over plasma has been attained (135).

Genetics.—PTC deficiency, like hemophilia, is believed to be inherited as

a sex-linked recessive characteristic. However, hemorrhagic manifestations appear to be more common in persons heterozygous for PTC. Hule & Nešpůrková have reported a patient whose mother and sister showed marked impairment of prothrombin consumption (150). Similar occurrences are not sufficiently common to be of real help in the identification of carriers (135). Sporadic cases of this disorder have about the same reported incidence as in hemophilia, 25 to 45 per cent (17, 151). As in hemophilia, the number will probably be reduced with careful survey of the pedigree of the proband.

Therapy.—Although prophylactic plasma transfusions have been used, it is generally believed that transfusion therapy should be used to treat hemorrhagic episodes when they occur. The corrective material is in the plasma. In the past it was suggested that PTC became activated on storage and that old plasma was superior to fresh plasma. Recent data indicate a progressive decline in PTC activity during storage. Brafield & Case (152) found little PTC activity in blood stored under the usual blood bank conditions for 14 days. Brinkhous has mentioned that plasma several months old is completely ineffective (153). Human serum transfusions appear to have no advantage over plasma (151, 152).

Diagnosis.—Definitive diagnosis depends on the failure of a patient's plasma to correct the coagulation defect of a previously diagnosed patient. A presumptive diagnosis is possible with the finding of a prolonged partial thromboplastin time, abnormal thromboplastin generation, or delayed prothrombin utilization and a normal prothrombin time. The coagulation defect must be corrected by serum from a normal individual, but not by normal plasma or serum which has been treated with $BaSO_4$. Mild deficiencies can be diagnosed only by the relative failure to correct the defect of an individual with a severe deficiency.

Vascular PTC Deficiency

The hemostatic defect of PTC deficiency is usually considered to be a defect of coagulation. A few reports of PTC deficiency associated with a prolonged bleeding time have appeared recently (10, 154, 155). The patient described by Combrisson-Le Bolloch *et al.* (155) also had a deficiency of "proconvertin" and should therefore be considered separately. The patients described by Soulier & Larrieu (10) and Sjølin & Videbaek (154) appear to have a defect analogous to vascular hemophilia. It is not clear as yet whether the existence of a vascular defect along with PTC deficiency is coincidental or whether this represents genetic linkage.

Parahemophilia and Factor V

Nomenclature.—This hemophilioid disease was named parahemophilia by Owren in his description of a hemorrhagic tendency due to the deficiency of a plasma protein which he termed Factor V (156). Like AHF, Factor V is not adsorbed readily by "prothrombin adsorbants" but, unlike hemo-

philia, parahemophilia is marked by a long prothrombin time. Many workers previously had suggested the existence of such a factor, but Quick showed conclusively that stored plasma was deficient in a nonprothrombin factor necessary for thrombin formation, which he termed labile factor (157). Fantl & Nance (158) observed that a prothrombin accelerator was needed to enhance the formation of thrombin from a prothrombin preparation. Ware, Guest & Seegers (159) isolated a similar material, essential for thrombin formation in a purified system, which they termed accelerator globulin (AcG). It is now generally assumed that these factors are identical but there is disagreement as to nomenclature. The terminology is further complicated by the thinking of some workers that an inactive substance (plasma AcG, proaccelerin) is transformed to an active substance (serum AcG, accelerin) during clotting. A rather complete list of presumed synonyms is given by Fantl (160).

Genetics.—The hereditary aspects of this disease have been reviewed by Graham (16, 161) and Fantl (160). The mode of transmission is not clear. It is of interest that in the study of Kingsley, all parents and all children of clinically affected persons were found to have a significant reduction of Factor V (162).

Pathophysiology of the defect.—Patients having this congenital defect have been reviewed recently by Larrieu and associates (163) and by Fantl (160). Four additional cases have been reported by Lewis and her co-workers (164). Acquired deficiency of this factor has been reviewed by Fantl (160) and found to be associated with hepatic disease, sepsis, scarlet fever, polycythemia vera, carcinoma of the prostate, and tuberculosis. Fantl reports that a hemorrhagic tendency occurs with levels below 30 per cent of normal (160).

Factor V deficiency affects the whole blood clotting time, partial thromboplastin time, prothrombin utilization, and characteristically the prothrombin time. It has been shown recently that Factor V is essential in the thromboplastin generation test (165, 166). Seegers *et al.* (167) believe that thromboplastin generation represents transformation of inactive (plasma) AcG to active (serum) AcG.

Normal platelets have been reported to contain a material (platelet factor 1) that is similar to serum AcG (168). It is now believed that this is not a specific platelet protein, but that it represents plasma protein adsorbed by platelets (169, 170, 171). Platelets from Factor V-deficient patients contain no accelerator activity but acquire the accelerator when exposed to normal plasma (170).

The study of Factor V activity in the blood of the newborn continues to be of interest. A recent study by Israels and his colleagues (172) indicates that Factor V levels in newborn human infants is low and that normal levels are reached by the sixth day of life. These results are in marked contrast to the findings of Fresh and associates who found that proaccelerin levels are above normal at birth (146). Capillary blood was used in one series

(146), while venous blood was used in the other series (172), and determinations were made by different procedures.

It is of interest that Factor V is present in plasma and lymph of all animals investigated (160). It has been shown repeatedly that although considerable activity is present in the serum of some animals, Factor V activity decreases during clotting of human blood. These studies have been confirmed by Douglas. Factor V consumption during clotting is retarded in bloods deficient in AHF, PTC, PTA, or platelets, and bloods from patients under therapy with heparin and phenylindanedione (173).

Chemical and physical characteristics.—Work is continuing on the purification of Factor V. A method based on chromatography using Amberlite resin has been reported by Cox, Lanchantin, & Ware (174). Human plasma exposed to Amberlite IR–400 loses little activity, while human serum activity is adsorbed and can be eluted. This technique has resulted in about a thousandfold purification of this catalytically active trace material. Characterization of the active material is difficult because of its lability. Although apparently not chemically pure, the major portion of its activity was found to migrate as a single component between gamma and beta globulin with zone electrophoresis on filter paper (174).

Several differences between human and bovine materials have been reported by Cox, Lanchantin & Ware (174). They note that $BaSO_4$ treatment of bovine serum increases its activity, while similar treatment of human serum removes all residual activity. Bovine serum activity cannot be adsorbed on Amberlite resin, while human serum activity is readily adsorbed (174).

A new assay procedure using a synthetic plasma substrate has been described by Seaman & Owren (175). It was found that Asolectin, a soybean phosphatide preparation, specifically binds and removes proaccelerin from normal plasma. Although the assay is not influenced by factors ordinarily removed by $BaSO_4$, Asolectin concentration is critical since in excess it also removes prothrombin and proconvertin (175).

Diagnosis.—The characteristic finding in parahemophilia is a prolonged prothrombin time which is corrected by fresh adsorbed normal plasma, but not by aged normal plasma. Prothrombin utilization during clotting is retarded. Mild deficiencies require a specific assay for diagnosis.

Management.—The only effective treatment for the hemorrhagic episodes associated with Factor V deficiency is the administration of fresh plasma. Intravenous injections are necessary since subcutaneous and intramuscular routes of administration will not produce levels sufficiently high for hemostasis. In order to obtain these, Fantl has found it is necessary to administer 10 ml. of fresh plasma per kg. of body weight (160). The frequency of administration depends upon the clinical response and the rate of disappearance from the circulation. Fantl has reported that half the injected activity remains after approximately 20 hr. (160).

SPCA and Stuart Factor and Their Deficiencies

Nomenclature.—In 1949 de Vries, Alexander & Goldstein (176) recognized a factor which shortened the prothrombin time of a mixture of aged normal plasma and fresh $BaSO_4$-treated plasma. This activity was present in serum as well as plasma and since it appeared to speed the conversion of prothrombin to thrombin was named serum prothrombin conversion accelerator (SPCA). Until recently it has been assumed that the effect of human serum on prothrombin time tests was due predominantly to this single factor. There has not been general agreement as to nomenclature but it has been suggested that the following commonly used terms are synonyms: serum prothrombin conversion accelerator (SPCA), Factor VII, convertin, and stable factor. These and other synonyms which are less commonly used are listed by Macfarlane (110).

A congenital defect of SPCA was described by Alexander and his associates (177) in 1951. Since that time additional patients have been reported from other laboratories. The characteristic finding in these patients is a long prothrombin time which is corrected by the addition of normal serum or plasma, but not by $BaSO_4$-treated plasma. Results of other tests of coagulation have appeared to be variable. Hougie, Barrow, & Graham (5) reviewed the previously reported cases and pointed out that two types of coagulation anomalies were represented. Some patients had abnormal thromboplastin generation and poor prothrombin utilization. Others with an equally long prothrombin time had normal thromboplastin generation and normal prothrombin utilization. Hougie *et al.* (5) restudied a patient previously reported to have hypoproconvertinemia (178). In direct mixing studies it was found that there was mutual correction of the prothrombin time defect of their patient and the patient described by Alexander (5, 179). It was proposed that their patient had a new coagulation defect, named the Stuart defect from the surname of the patient (5). Biggs (180), Greig & Tattersall (181), Telfer, Denson & Wright (182), and Duckert (183) have also found evidence of a new coagulation defect.

It is impossible at this time to evaluate the numerous articles describing activities attributed to SPCA, convertin, or Factor VII since it has been pointed out that the assay procedures are sensitive to changes in levels of both SPCA and Stuart factor (5). For this reason much of the recent literature on these subjects is omitted.

SPCA deficiency.—The patient originally described by Alexander is the prototype of this disease (177). This deficiency manifests itself with a long prothrombin time in the presence of tissue thromboplastin. The factor is not necessary for normal partial thromboplastin time (184), thromboplastin generation, prothrombin utilization, or recalcified clotting time. Russell's viper venom is reported to correct the prothrombin time defect (5). Before identity can be established, all cases hitherto reported must be carefully restudied. However, with the information now available, the

patients described by the following workers appear to have the same defect: Jürgens (185), Koch *et al.* (186), Hicks (187), Owren (188), and Jenkins (189) restudied by Ackroyd (190).

Stuart factor deficiency.—The patient, Stuart, is taken as the prototype (5). Plasma with a lack of Stuart factor gives a long prothrombin time in the presence of tissue thromboplastin, defective thromboplastin generation, a long partial thromboplastin time, a long recalcified clotting time, and impaired prothrombin utilization. Russell's viper venom fails to correct the abnormal prothrombin time defect.

Several patients previously reported have been restudied by direct plasma mixing experiments. Graham has found the patients described by Barnett (191) and Crockett *et al.* (192) to have the same defect as does Mr. Stuart (5, 44). Using a sample of Mr. Stuart's plasma, Koller found that a patient he described with Bachmann (193) and the patient reported by Telfer *et al.* (182) have the Stuart defect (194).

Graham, Barrow & Hougie have studied the family members of their patient, Stuart (6). They found that the deficiency was inherited as a highly penetrant, but incompletely recessive, autosomal characteristic. Mild prolongation of prothrombin time was found in persons heterozygous for the defect.

Chemical, biological, and physical characteristics of these factors.—It now appears that at least three $BaSO_4$ adsorbable factors influencing the prothrombin time are decreased by administration of Dicumarol and related compounds. Factor VII is decreased rapidly by these compounds, but rises quickly with Vitamin K therapy (194). Prothrombin and Stuart factor decrease more slowly with these compounds and rise more slowly with Vitamin K therapy (194).

Seegers and his associates (195) have studied the plasma of Alexander's SPCA-deficient patient in their purified clotting system. Autoprothrombin derived from prothrombin by means of platelet factor 3 is reported to supply the same activity as SPCA (195). They consider that this finding establishes the derivation of SPCA from the prothrombin molecule. Carter & Warner's amperometric analyses of thrombin, prothrombin, and autoprothrombin for sulfhydral and disulfide linkages support the idea (196). Goldstein & Alexander reported that in the absence of proconvertin, prothrombin will not form thrombin with tissue thromboplastin, but that proconvertin-free prothrombin is readily converted to thrombin if platelets are used for thromboplastin (179). Final interpretation of the perplexing problems resulting from these important observations must await further work.

Plasma Thromboplastin Antecedent

Nomenclature.—Plasma thromboplastin antecedent (PTA) deficiency was described in 1953 by Rosenthal, Dreskin & Rosenthal (197). It is a mild hemorrhagic bleeding tendency thought to be due to the lack of a specific

factor (PTA) necessary for blood coagulation and hemostasis. The name Hemophilia C has been used as a synonym (198).

Pathophysiology.—Previously reported cases with a deficiency of this factor have been reviewed by Caen & Bernard (199). Additional cases have been reported by Gouttas (198), Campbell (200), Stegelske (201) and their collaborators. Although patients with a deficiency of this factor have a bleeding tendency, the symptoms are usually less severe than in hemophilia (202). The deficiency is not necessarily complete; mild symptoms are associated with such a partial defect. The deficiency characteristically gives an abnormally short serum prothrombin time, a long partial thromboplastin time, and incomplete thromboplastin generation. On the other hand, the prothrombin time, platelet number, bleeding time, and capillary fragility are not influenced by an absence of this factor.

It is generally assumed that this disease represents the deficiency of a single coagulation factor. Numerous investigators have shown that PTA-deficient plasma corrects the coagulation defects of hemophilia and PTC deficiency. One of Rosenthal's patients studied in our laboratory had a plasma AHF level greater than normal. However, Ingram has suggested that these patients represent multiple mild deficiencies of other coagulation factors (203); Seegers & Johnson have proposed that this disease represents a deficiency of platelet cofactor I along with a defect in the formation of autoprothrombin II (131).

Genetics.—PTA deficiency is transmitted as an autosomal dominant trait with a probable high degree of penetrance and variable expression of the gene (204). Variable degrees of the defect in a single pedigree have been noted (205).

Chemical and physical characteristics.—PTA activity is present in both normal plasma and serum. The corrective principle appears to be relatively stable although divergent results are reported. On studying its thermal inactivation, Rosenthal (206) found that the activity remained after heating to 60°C. for 10 min. This conflicts with Ramot, Angelopoulos & Singer, who found activity markedly decreased when plasma was heated to 58°C. for 10 min. (207). Plasma frozen for two years or stored at room temperature for four months retains its activity (206). Rosenthal has reported that plasma PTA activity increases during storage (206). This is based on the finding that fresh plasma from a patient with a mild deficiency failed to correct the abnormal serum prothrombin time of a patient with a marked deficiency, but the identical plasma, after being frozen for 4 or 64 days, corrected the serum prothrombin time of a similar patient. This effect was not seen by Ramot, Angelopoulos & Singer (207).

Attempts to characterize PTA have been partially effective. Seitz filtration removes some activity from normal plasma. Adsorption of plasma with $BaSO_4$ has not shown clear-cut separation. PTA activity is present in the supernatant plasma, the saline wash of the precipitate, and the citrate eluate

of the precipitate (206). Since PTA activity is present in both serum and plasma, the thromboplastin generation test is normal if either of these components is obtained from a normal subject (207). Stegelske *et al.* (201) found that both serum and plasma from their patient gave abnormal thromboplastin generation. This type of finding is consistent with Hougie's criteria for inhibitors (208). Fractionation by $(NH_4)_2SO_4$ has been partially effective as a means of characterizing PTA. Minimal activity is reported in a 0 to 25 per cent fraction by Rosenthal (206), while Ramot *et al.* (207) found marked activity in the same fraction. Both groups of workers agree that maximal activity is present in the 20 to 30 per cent $(NH_4)_2SO_4$ fraction of normal plasma (206, 207). Activity of various Cohn fractions is reported to be variable, but maximal activity is said to be in the Fraction IV–1 (207). With paper electrophoresis, PTA activity is reported to migrate in the area between gamma and beta globulins (198, 206). It has been reported that PTA is decreased during Dicumarol therapy, in chronic liver disease, and in avitaminosis K (140). The possible influence of Stuart factor in the assays used must be studied.

Diagnosis.—Definitive diagnosis of PTA deficiency is made on the failure of a patient's plasma to correct the defect of a previously diagnosed patient. Presumptive diagnosis is made if both $BaSO_4$-treated normal plasma and normal serum correct the patient's coagulation defect. It has been suggested that PTA deficiency is indicated if the addition of $BaSO_4$-treated normal serum to patient's serum corrects the thromboplastin generation test (209). Ramot *et al.* (207) found that mild deficiencies can be detected by the thromboplastin generation test even when the serum prothrombin time is normal. Rosenthal reports that in some mild cases the thromboplastin generation test is normal, and the defect is detected only by the failure of the plasma in question to correct the abnormal serum prothrombin time of a defective patient (205). Diagnosis is further complicated by the finding that stored plasma will correct the serum prothrombin time of the donor patient (205).

Management.—Rosenthal has discussed the management of the bleeding tendency of this hemophilioid disease (205). Blood bank plasma less than 14 days old has been found to be satisfactory for transfusion therapy. The effect of a transfusion gradually disappears over a one-week period if measured by the correction of the patient's whole blood clotting time. However, the patient's serum prothrombin time is corrected only transiently. It is recommended that if surgical procedures are necessary, sufficient plasma to give a 15 per cent volume should be administered prior to surgery (205).

Hageman Trait

Nomenclature.—In 1955, Ratnoff & Colopy fully described an asymptomatic disorder of blood coagulation which was named "Hageman trait" after the surname of the first patient (210). Hageman trait is thought to be due to the lack of a specific (Hageman) factor, which is necessary for *in vitro*

blood coagulation (211). Its role in hemostasis is not at all clear. An identical disorder has been observed in patients by other investigators (212, 213, 214).

Pathophysiology of the defect.—The patients with Hageman trait have no symptoms of a bleeding tendency. In most cases, the trait has been discovered as the result of routine coagulation studies being done prior to anticipated surgical procedures. In spite of abnormal coagulation studies, these patients appear to have no hemorrhagic complications following surgery.

The clotting time of whole blood is usually abnormally long in either plain glass or siliconized tubes (215). The recalcified clotting time of plasma, the serum prothrombin time, thromboplastin generation (212), and the partial thromboplastin time (213) are also abnormal in patients with this defect.

Prothrombin time is usually normal but may be slightly prolonged (213). Bleeding time, fibrinogen, and capillary fragility are not influenced by a deficiency of this factor.

In a series of tests, Frick & Hagen (214) found that plasma from patients known to be deficient in AHF, PTC, or PTA correct the whole blood clotting time, serum prothrombin time, 2-stage prothrombin utilization, and recalcified clotting time of blood deficient in the Hageman factor. However, plasma from their patient with the Hageman trait failed to correct the defective serum prothrombin time and whole blood clotting time of patients known to be deficient in AHF, PTC, or PTA (214). In similar mixing experiments, 2-stage prothrombin utilization of AHF-, PTC-, or PTA-deficient blood was corrected by plasma from the patient with the Hageman trait (214). These findings are not easily explained on the basis of experience with other types of plasma.

Chemical and physical characteristics.—Hageman factor is present in human plasma and serum, and $BaSO_4$-treated plasma and serum. It does not pass a dialysis membrane (214). It is relatively heat stable, remaining active at 56°C. for 30 min.; however, there is partial destruction after 15 min. 65°C. (214). Electrophoretic studies indicate that most of the activity is in the beta globulin fraction.

A 500-fold concentration as compared with the original normal serum is reported by Ratnoff & Margolius (215, 216). The procedure for concentration consists of precipitation of $BaSO_4$-treated serum with $(NH_4)_2SO_4$ between 30 and 40 per cent saturation. A corrective activity was adsorbed at pH 5.2 onto kaolin and eluted selectively at pH 9 with a mixture of tris buffer and $(NH_4)_2SO_4$. This material not only corrects Hageman-deficient plasma, but accelerates clotting and prothrombin utilization of normal blood.

The factor has also been found to be present in blood of the rat, rabbit, mouse, guinea pig, sheep, and dog. It is lacking in Peking ducks (217) and horses (134). Sjølin (134) has found that freezing and thawing of platelet-rich, Hageman-defiicient plasma results in a correction of the defect. The

same treatment of platelet-poor plasma results in no change in activity.

Diagnosis.—In the absence of known deficient plasma, diagnosis is difficult. It is to be strongly suspected when abnormal coagulation tests are found in a patient with no known bleeding tendency.

A quantitative assay for Hageman factor has been described by Margolius & Ratnoff (218). This is based on the ability of normal plasma to correct the recalcified clotting time of Hageman-deficient plasma. In this system normal oxalated plasma diluted 160 times with buffer completely corrects the recalcified clotting time of Hageman-deficient plasma. Patients with severe hepatic deficiency were found to have from one-fourth to one-half the activity of normal subjects.

Genetics.—Hageman trait has not been found in any parent or offspring of any patient with the defect. Although it has been seen in two sisters, all other members of their large family were found to have normal amounts of Hageman factor (218). Ratnoff & Margolius believe that Hageman trait is transmitted as an autosomal recessive trait (218).

Management.—The transfusion of 50 ml. of blood 20 days old corrected the whole blood clotting time, the serum prothrombin time, and the thromboplastin generation test of a patient with Hageman trait (212). However, transfusion therapy is not necessary once the diagnosis is firmly established since the occurrence of excessive bleeding is no more likely than in a normal individual.

Tetartohemophilia

(Deficiency of Fourth Thromboplastic Factor or PTF-D)

This seemingly new entity, believed to be a deficiency of a specific plasma protein, was described several years ago (219). A restudy of this patient in several laboratories has shown that the patient suffered from mild Christmas disease with a mild circulating anticoagulant (44, 220).

Multiple Hereditary Deficiencies

It is recognized that multiple deficiencies of coagulation factors can occur as a result of drug therapy or pathologic conditions. With the increasing recognition of newer clotting factors, reports are appearing of congenital deficiencies of more than one factor. The difficulties of diagnosis of a single deficiency are magnified many-fold by the possibility of two or more defects. Presumptive diagnostic criteria for hemophilia and the hemophilioid states are based on the characteristics of a single deficiency. Before the existence of more than one deficiency can be established, each factor must be evaluated with a specific quantitative assay. It is generally recognized that specific quantitative assays are available only for the determination of prothrombin, fibrinogen, AHF, and AcG, but these are not widely used. The presence of a circulating anticoagulant in the presence of a single deficiency can appear to represent a multiple deficiency state. Many of these problems and the genetic aspects of multiple hereditary deficiencies have been discussed recently by Graham (161).

Combined AHF and PTC deficiency.—Five cases have been reported to have a combined deficiency of AHF and PTC (203, 221, 222, 223). The patient described by Ingram is unique in that in addition to partial deficiencies of AHF and PTC the patient had a prolonged bleeding time (203). Graham, in reviewing the other cases, indicated that only one of those seemed to fulfill most of the criteria necessary for such a diagnosis (161). It is pointed out that even this report (223) did not include information on the effect of the patient's serum on the defect of a previously established PTC-deficient plasma (161). Recently, Graham has restudied two of the patients (221) and could demonstrate only AHF deficiency (44).

Combined hemophilia and parahemophilia.—Three patients have been reported to have combined deficiencies of AHF and Factor V (224, 225). Such a combination presents a difficult problem in diagnosis, since both factors are labile and although not absorbed from normal plasma by the usual "prothrombin adsorbants" are partially adsorbed by $Al(OH)_3$. Although normal AHF activity was found in the Factor V-deficient patient studied by the reviewers (226), the lability of Factor V, in the hemophilic plasma substrate, is one of the most troublesome features of the assay procedures for AHF. Graham points out additional reasons for his qualified acceptance of the probability that these three patients are unequivocally deficient in both factors (161).

Combined PTC and Factor VII (SPCA) deficiency.—During the past few years several patients have been reported to have a deficiency of both PTC and Factor VII (155, 227, 228). One patient also had an abnormal bleeding time (155). The criterion for the diagnosis has been the presence of a long prothrombin time in association with abnormal serum reactivity in the thromboplastin generation test. It has been pointed out that this pattern is typically seen in Stuart deficiency (5, 17). Deutsch has stated that it is possible that the cases of the previously described combined deficiencies of PTC and Factor VII are in reality cases of Stuart factor deficiency (17).

Other combinations.—Single descriptions of other combined defects have appeared. Scardigli & Guidi (229) have reported some members of one family to have deficiencies of AHF while other members of the same family are deficient in PTA. Newcomb and his co-workers have reported a patient with a congenital defect similar to that of acquired Dicumarol toxicity (230).

Circulating Anticoagulants

Since Hougie's review in 1955 (208) many papers have appeared describing spontaneously occurring circulating anticoagulants other than heparin or heparin-like inhibitors. These anticoagulants are of interest because they can cause severe symptoms, because of fairly frequent occurrence, and because they further complicate the already difficult problems of diagnosis and management.

Anticoagulant acting against AHF.—The development of a circulating

anticoagulant in a hemophiliac was given a classical study by Munro (231). This condition is also called refractory hemophilia. There may be a variety of anticoagulants in this category. Certainly there are a variety of ideas proposed concerning action, chemical nature, and origin of the inhibitors.

Rosenthal has followed the development of a refractory state in mild hemophilia (232). Lewis, Ferguson & Arends (233) have observed an inhibitor which acted against AHF in five cases of hemophilia. Bergna & Pavlovsky (234) have found inhibitors in two of thirty-four hemophiliacs studied [see also (235, 236)]. Verstraete & Vandenbroucke (29, 237) described a normal adult male who developed a circulating anticoagulant acting against AHF. The inhibitor had properties similar to an inhibitor in one of their hemophilic patients.

Perhaps because different patients are being studied, there is much disagreement about the nature of the anticoagulants in these conditions. In accord with the old antibody hypothesis, Richards & Spaet have demonstrated that a human AHF preparation is antigenic in the rabbit (238). The rabbit antibody produced had anticoagulant activity and was similar in physical properties to antibody-type inhibitors previously reported in humans. It was suggested that there may be a series of different AHF proteins, analogous to the different kinds of human hemoglobin (238). Windorfer, Schultze & Schwick could not demonstrate an antibody with whole serum from a patient with an inhibitor (235). However, when the inhibitor was fractionated from serum with zone electrophoresis, these workers showed an antigen-antibody reaction in the two fractions with the greatest inhibitor activity.

The problem of false positive precipitin studies with AHF was discussed by Penalver and his co-workers. They were unable to demonstrate antibodies in refractory hemophilia (239). Deutsch has commented on these findings (17).

Speer and his associates have produced evidence for a lipide inhibitor in a boy with classical hemophilia (240). Although the patient's serum gave normal thromboplastin generation when other components used were normal, the patient's plasma delayed the recalcification time of normal plasma.

Anticoagulant acting against PTC.—In 1953, Lewis & Ferguson described a PTC-deficient patient who developed a circulating anticoagulant after transfusion therapy (241). The inhibitor was later shown to act against PTC (233). When the inhibitor was present at a high titer, electrophoresis showed that gamma globulin was elevated to 35 per cent of the total protein. Four months later the inhibitor was markedly decreased and the gamma globulin level had dropped to 18 per cent of the total protein. [For similar patients, see references (234 and 236)]. Fantl and his co-workers have also described beta-prothromboplastin deficiency (PTC deficiency) with an anticoagulant (242, 243). They made the interesting suggestion that there may be two types of deficiencies. One type of defi-

ciency would be a total lack of the protein factor in question; this type would be likely to form antibodies after transfusion of normal plasma which contains the missing factor. The other deficiency would be functional: a patient with an abnormal protein closely related in antigenic properties to a clotting factor, but without blood clotting function, would not form antibodies.

A human serum "PTC" preparation was shown to be antigenic to rabbits by Lewis & Didisheim (244). The rabbit antibodies produced inhibited human PTC and human proconvertin.

Anticoagulant acting against Factor V.—Hörder has described the first case of a familial deficiency of Factor V accompanied by a familial inhibitor of Factor V (245). Inhibition of Factor V required a 10 min. incubation time. The inhibitor was not adsorbed by $BaSO_4$ and was stable at 56°C. for 30 min. Inhibitor was removed from plasma with petroleum ether and the ether residue was active. The serum was stated to be almost devoid of inhibitor activity (246).

Ferguson, Johnston, & Howell have given the first description of an inhibitor against AcG (Factor V) appearing spontaneously in a previously normal patient (247). Most of the properties of the inhibitor agree with the data reported by Hörder & Sokal (246). In addition to the tests which one would expect to be abnormal, the following results were obtained: (*a*) abnormal thromboplastin generation with patient's serum; (*b*) failure of patient's plasma to correct either the partial thromboplastin time or thromboplastin generation test of hemophilic, aged, Stuart-deficient, or PTC-deficient plasmas. Thus, the authors point out that all clotting tests must be interpreted very cautiously when a circulating anticoagulant is present in the plasma. They also pointed out that the antithromboplastin of many workers may prove to be anti-AcG, if their sole diagnostic criterion was a relatively prolonged clotting time of their test plasma with dilute thromboplastin (247).

Anticoagulant in SPCA deficiency.—Campbell, Unugur, & Fudenberg (248) have made a preliminary report concerning the development of an anticoagulant in a patient with a 15 to 20 per cent level of SPCA.

Anticoagulants associated with systemic collagen diseases.—Frick has reported that a circulating anticoagulant was found in three patients out of thirty studied with probable collagen diseases. The most interesting of these patients was a woman who gave birth to an infant in whom an inhibitor was detectable for seven weeks after birth (249). Lee & Sanders demonstrated an anticoagulant in seven out of forty-three cases of collagen disease (250). This appears to be a conservative estimate for their group, as nine patients had a prolonged prothrombin time, and twelve had an abnormally prolonged prothrombin time with dilute thromboplastin.

For other examples of circulating anticoagulants in the collagen diseases see Swift (251), Meacham & Weisberger (252), Bonnin and co-

workers (253), Ramot & Singer (254), Laurell & Nilsson (255), and Alagille, Crosnier & Soulier (256).

Miscellaneous inhibitors.—A very potent anticoagulant that neutralized AHF and PTC was found in a female 15 years after an uneventful pregnancy and delivery (233). Benthaus & Richter described an inhibitor in a patient with pemphigus (257).

Long and his co-workers showed that plasma of a patient with macroglobulinemia contained an inhibitor (258). Precipitation of the macroglobulins by addition of distilled water also precipitated the inhibitor, which the authors believed acted as an antiproconvertin and an antiproaccelerin. The preliminary report of Henstell & Feinstein is not in accord with these findings (259).

Diagnosis.—If normal plasma does not correct the clotting defect of the patient's plasma in clotting tests, an inhibitor is indicated rather than a double defect (234). Likewise, if both $Al(OH)_3$-treated patient's plasma and patient's serum give abnormal thromboplastin generation when other reagents added are normal, an anticoagulant is indicated (208). Bergna & Pavlovsky have described a globulin precipitation test that leaves the anticoagulant in the supernatant. Tests of the precipitate can then be used to determine the primary deficiency (234).

Treatment.—When transfusion therapy is used for a hemorrhagic episode in a patient with a deficiency disease, a circulating anticoagulant may occur. Treatment once begun should be vigorous in order to stop bleeding before an anticoagulant can develop. If there is previous history of the development of a circulating anticoagulant with transfusion therapy, treatment, if used at all, must be vigorous. In some patients there is regularly a four to six-day time-lag after transfusions are begun before the inhibitor develops. Appearance of the inhibitor can be detected by the increase of the partial thromboplastin time of a mixture of equal parts of normal plasma and patient's plasma, and can be followed by doing this test daily (260). Washed red cells are used to maintain the hematocrit when the use of plasma is contraindicated.

Comment

During the period covered by this review, numerous articles on the subject of hemostatic disorders have appeared written by workers in all fields of scientific investigation. Many of these have furnished a stronger basis for older concepts, but many others have indicated that earlier assumptions must be revised. The descriptions of Hageman trait and Stuart deficiency are of particular interest. Although numerous interesting problems are presented by the Hageman trait, one of major importance is the finding that a patient can have a marked defect of the coagulation mechanism yet have none of the clinical manifestations of a bleeding tendency. The description of the Stuart defect points out that general agreement can not replace careful experimental observation.

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NUTRITION AND NUTRITIONAL DEFICIENCY DISEASES[1,2]

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Introduction

During the past few years, two principal items of our diet have come under close scrutiny. These are fats and fatty acids, and protein and amino acids. A great deal of research has been done on (*a*) the relationship of fats and cholesterol to arteriosclerosis; (*b*) the metabolism of the fatty acids; (*c*) the minimum essential amino acid requirements; (*d*) the question of supplementation of cereals with amino acids; and (*e*) the relationship of amino acids to hepatic encephalopathy. Though these subjects are still highly controversial, sufficient data have been accumulated to justify a review of present concepts, and of the facts on which these concepts are based. The role of pantothenic acid in human nutrition has been investigated with the help of the metabolic antagonist, ω-methylpantothenic acid, and a good deal of interesting information has been recorded. These subjects will form the substance of this review. If concepts described on these pages lose validity before this volume is published, the authors can only apologize for having the temerity to review such active and rapidly changing areas in the field of nutrition.

Fats and Fatty Acids

Any physician who has traveled to underprivileged areas of the world where little animal fat is eaten, has been impressed by the scarcity of arteriosclerotic lesions, particularly of the coronary arteries, in autopsy material. This impression has been confirmed by studies reported by Higginson & Pepler (1). Such observations and the impression that high fat diets, obesity, and a high incidence of arteriosclerosis go hand-in-hand, particularly in the United States, have stimulated numerous studies on these aspects of the arteriosclerosis problem. Though these studies seem to indicate that nutrition plays a considerable role in this important health problem, many other factors are quite important, also, and these must not be forgotten in our enthusiasm for the nutritional aspects. Genetic and hormonal factors play very significant roles. Muscular activity may also play

[1] The survey of the literature pertaining to this review was concluded in June, 1957.

[2] The following abbreviations have been used: ACTH (adrenocorticotropin); DPN (diphosphopyridine nucleotide); DPNH (diphosphopyridine nucleotide, reduced); TPN (triphosphopyridine nucleotide); TPNH (triphosphopyridine nucleotide, reduced); PABA (para-aminobenzoic acid).

a part and there are probably many other important influences. In this review, however, only the nutritional factors will be covered.

By numerous and extensive epidemiologic studies, Keys and his associates have demonstrated that a positive correlation exists between the amount of dietary fat, the level of blood cholesterol and cholesterol-carrying β-lipoproteins, and the degree of coronary artery disease in various population groups. Obesity per se does not seem to play as significant a role though, clearly, a high fat diet tends to induce obesity. The differences in the mortality rates due to coronary disease between the United States, England, and Italy do not correlate with the weight differences of middle-aged men in these countries (2). In one study (3), the dietary fat intake and the blood cholesterol levels were investigated in Americans, Englishmen, Norwegians, Neapolitans, and three groups of people from the Cape Town area. Americans and Cape Town inhabitants of European descent had the highest fat intakes. Cape Town Bantus had the lowest. The other groups had decreasing amounts of fat in their diets in the order in which they are listed. Cholesterol levels were highest in those groups with the highest dietary fat content. Death rates from coronary artery disease were proportional to the cholesterol levels of the groups. In another study (4), the dietary fat and cholesterol levels of three groups of people were compared. These groups included experimental subjects from the Hastings State Hospital in Minnesota; normal men from the United States, Italy, Sweden, South Africa, Spain, and England; and ambulatory patients with definite coronary disease. From this study the investigators concluded that diets high in fat led to high blood cholesterol levels and that reduction in fat calories brought about a reduction in cholesterol levels. Such data have led Keys and his group to propose that the quantity of fat in the diet may be the most important nongenetic factor affecting the level of cholesterol in the serum of man (5). Similar conclusions have been reached by others (6 to 9).

Bersohn & Wayburne (10) and Rafstedt (11) found that the cholesterol levels of newborn infants were 71 to 75 mg. per 100 ml. and rose rapidly on ordinary diets in the first four days. No increase occurred when pure carbohydrate was fed. Cholesterol levels of newborn infants were very similar even though the cholesterol levels of the mothers differed greatly.

Some investigators have questioned the supposedly great increases of animal fat in the American diet during the past 50 years. Though more fat is purchased, a great deal is discarded or thrown out. Very little is saved as in former years for use in cooking. Nonetheless, the American diet has one of the highest fat contents of any diet in the world and Americans have the highest incidence of coronary disease.

One must remember, in interpreting all these results, that a relationship between high fat diets and hypercholesterolemia has indeed been proved. However, the relationship between hypercholesterolemia and coronary arteriosclerosis is based on circumstantial evidence. Hypercholesterolemic

states associated with diabetes, nephrotic syndrome, and hypothyroidism in human beings are frequently followed by coronary arteriosclerosis but investigators may not induce coronary arteriosclerosis in man by artificial long-continued hypercholesterolemia. When they perform this experiment in rats or dogs by feeding cholesterol and thiouracil, coronary artery occlusion seldom occurs. Investigators attempting to produce pulmonary arteriosclerosis in rabbits have fed high-fat diets and injected small blood clots into the venous circulation (12), thus blocking pulmonary arteries and inducing pulmonary hypertension. Only under such artificial circumstances did fat appear in fibrous intimal thickenings of the pulmonary arteries. It did not appear in the pulmonary arterial walls of rabbits on low-fat diets. However, by none of these means have the vascular diseases of man and their lethal consequences been duplicated exactly in laboratory animals.

Still focusing on blood cholesterol levels, investigators have tracked down the factors in vegetable diets that appear to lower blood cholesterol. Kinsell and his associates (13) in 1952 showed that diets containing large amounts of vegetable fats lowered the blood cholesterol levels. Later they went on to show that this effect was not due to the low cholesterol level of the diet, or to sitosterol-like compounds in it, but in all likelihood, to the polyunsaturated fatty acids (14, 15). Beveridge (16, 17) investigated the effects of varying amounts of fat from animal and vegetable sources with and without added cholesterol on the blood cholesterol levels of five healthy men. When 28.5 per cent of calories were supplied by vegetable fat, cholesterol levels decreased 35 mg. per 100 ml. from the amounts found on the customary diet. When 200 mg. of cholesterol was added to this vegetable fat diet, the decrease in cholesterol was 27 mg. per 100 ml. When vegetable fat was increased to 58.5 per cent of the calories, cholesterol levels decreased 47 mg. per 100 ml. When, in subsequent studies, 58.5 per cent of the calories were derived from butter fat, lard, chicken fat, or beef drippings, there were increases in cholesterol ranging from 7 to 22 per cent. In a recent publication, Beveridge reports the evidence that this effect is due to the plant sitosterols rather than the polyunsaturated fatty acids (18). Bronte-Stewart and his associates (19) have compared cholesterol levels of five Bantus and two Europeans. When the Bantus, whose usual diet contains about 3 per cent fat, were given animal fat or hydrogenated nut oil, the cholesterol levels rose. When the Europeans were given vegetable fat (sunflower seed oil) or the unsaturated components of the sunflower seed oil, cholesterol levels fell; when the saturated components of the oil were given, cholesterol levels rose. These authors suggest that 27 per cent of the fat intake should be linoleate to prevent a rise in the serum cholesterol when abundant animal fat or cholesterol is given. Nyrop (20) has made a slightly lower estimate. The lowering effect of vegetable fats and the polyunsaturated fatty acids on blood cholesterol has been confirmed by many other investigators (21). Even in rabbits fed cholesterol (22) and in rats fed on high cholesterol, sulfur amino acid-deficient diets (23), linoleic

acid will lower cholesterol and prevent deposition of this material in the aorta. However, Keys (24) objects to the concept that atherosclerosis may be the result of polyunsaturated fatty acid deficiency on the grounds that animals with such deficiency states do not develop arterial lesions. Nor can the high incidence of atherosclerosis in the United States be ascribed to such a deficiency since the estimated intake of unsaturated fatty acids has decreased only from 14 per cent to 12 per cent in the last 50 years (25), or perhaps increased (26, 27). Furthermore, it is not clear whether lowering of the cholesterol level is always beneficial. For instance, the polyunsaturated fatty acids raise liver cholesterol in rats as the blood cholesterol is lowered (28). Saturated fats induce the opposite effect. Preliminary data in human beings fed low-protein or lipotropic diets suggest that dietary proteins under certain circumstances may determine the height of serum cholesterol levels (29).

Other methods of lowering serum cholesterol have been investigated. Niacin (30, 31) (but not nicotinamide) in 3 to 4 gm. doses per day, sitosterol (32, 33), a period of weight loss (34), and physical exercise (35) have been reported to lower cholesterol levels. Cholesterol from exogenous sources raises the blood cholesterol levels of human beings very little and only after a prolonged period of cholesterol feeding (36). Lipotropic agents have little, if any, effect on the blood cholesterol or on the arteriosclerotic process in man (37), but in animals choline deficiency results in arteriosclerosis and fatty liver. Feeding choline accentuates the arterial damage but removes the fat from the liver and reduces blood cholesterol levels. Cold environment plus choline deficiency also causes severe arterial damage (38, 39, 40).

Studies such as those described above have stimulated investigation concerning the absorption, transport and metabolism of fats and fatty acids, and the function of the polyunsaturated fatty acids. Patients with chylothorax or thoracic duct fistulae have been utilized for the absorption studies. When no fat is supplied in the diet, the chyle has the color and composition of serum. Fatty acids containing 12 to 18 carbon atoms and the polyunsaturated acids were absorbed well (41). The fatty acids of 8 to 10 carbon atom chain length were absorbed poorly. Most, if not all, triglycerides and diglycerides must be hydrolyzed for optimum absorption (42). Plant sterols compete with cholesterol for limited intestinal absorptive surface and may prevent absorption of cholesterol but in rabbits are absorbed to the extent of 0.1 to 1.0 per cent and appear in atheromatous plaques (43). Rancid fats with high iodine numbers and high degrees of polymerization are very toxic to rats (44, 45). Fats fed to chronically malnourished children are well absorbed, and do not cause steatorrheic diarrhea (46).

When serum of persons in the postabsorptive state is spun in the centrifuge, a milky supernatant and a clear subnatant fraction will be found. Most of the neutral fat is in the supernatant fraction though as much as

10 m.eq. per 1. may be present in the subnatant. Cholesterol and phospholipides are divided between the two layers about equally. The supernatant contains the chylomicrons with cholesterol and phospholipides dissolved in free fat. The subnatant layer contains fat held in solution by combination with proteins (47).

When heparin is administered to persons with postabsorptive lipemia, clearing of the serum usually occurs, due, it is postulated, to activation of lipoprotein lipase. Triglycerides of the chylomicrons are hydrolyzed by this enzyme to unesterified fatty acids which combine with albumin in the serum. These unesterified fatty acids may be released by lipoprotein lipase (48) of the adipose tissues also. This unesterified fraction which exists in plasma only for a matter of minutes is considered to represent the metabolically active fraction of the plasma lipides. The fasting state or uncontrolled diabetes elevates the level of these fatty acids, while a mixed meal, glucose or glucagon in the normal person, and insulin or tolbutamide treatment of the diabetic, results in a drop in the unesterified fatty acid level (49, 50, 51). Utilization of carbohydrate inhibits release of these fatty acids from fat depots. Depression of carbohydrate oxidation stimulates release.

The formation of fatty acids and cholesterol is dependent upon the metabolism of carbohydrate and the availability of coenzyme A (52). Starvation or caloric restriction abolishes the *in vitro* synthesis of these substances by liver slices (53). Other *in vitro* studies indicate that stimulation of the hexose monophosphate shunt by TPN increases fatty acid and cholesterol synthesis strikingly. Apparently, these synthetic reactions are TPNH rather than DPNH-dependent, since stimulation of the Emden-Myerhof reaction by DPN stimulates them very little (54). The enzymes necessary for these synthetic reactions may be found in mitochondria, microsomes, and the supernatant fraction obtained after centrifugal precipitation of the former two fractions. Starvation of the animal depresses the level of these enzymes or may result in the production of inhibitors. (55).

The mode of formation of the polyunsaturated fatty acid, arachidonic acid, from linoleic acid has been investigated by the use of C_{14}-labeled linoleic acid. An acetate radical, split from one molecule of linoleic acid, adds on to another to form arachidonic acid (56). During starvation periods, this process is replaced by another which results in the formation of 5,8,11-eicosa-trienoic acid, rather than linolenic acid as previously thought (57).

One of the metabolic roles of the polyunsaturated fatty acids is now considered to be stimulation of oxidative phosphorylation which becomes uncoupled during a deficiency of these essential fatty acids. Activity of cytochrome-*c* oxidase is increased whereas the oxidations of reduced cytochrome-*c* and DPNH are decreased. The ratio of phosphate incorporated to oxygen utilized (P:O ratio) is reduced. In the animals under investigation, a deficiency of vitamin B_6 merely accentuated these effects

of the deficiency of fatty acids (58, 59). Lipides of the polyunsaturated type play an important role in the activity of the cytochrome components in biologic oxidation. The main site of action of the polyunsaturated fatty acids is the phosphate esterification system, coupled with the oxidation of reduced cytochrome-*c*.

The metabolism of cholesterol in the human being has also been studied. The liver-plasma cholesterol pool is 20 to 30 gm. with an average turnover time of 8 to 12 days. Each day, 2 to 3 gm. are used to form bile acids, steroids, etc. Two grams of the cholesterol metabolized have been synthesized *in vitro*—0 to 1 gm. has been derived from the diet (60). Cholesterol injected into the blood is excreted rapidly in the bile as bile acids (61). Though a monkey fed a high (70 per cent) fat diet and 6.51 gm. of cholesterol per day, for 1388 days developed xanthomas, arteriosclerosis, and very high blood cholesterol levels (62), Keys (36) was not able to demonstrate a relationship between dietary cholesterol intake and blood cholesterol levels in human beings.

There has been considerable investigation on the effect of diets rich in different types of fats on the growth rate and length of survival of rats. In general, butterfat and lard increased the growth rate and decreased longevity while fats rich in unsaturated fatty acids had the opposite effect (63, 64). Those fats which increased the growth rate also increased the food intake of the rats and vice versa. Apparently, optimum growth is not necessarily maximum growth. The most satisfactory growth rates resulted from a low ratio of saturated to unsaturated fatty acids (65). The polyunsaturated fatty acids also appear to have a lipotropic effect and to protect rats from fatty liver, while saturated fats do not (66).

Polyunsaturated fatty acids are a requirement for infants. When such subjects are fed a milk mixture in which fat comprises less than 1 per cent of the calories, frequent stools, perineal itching, and thickening of the skin develops. Linoleic and arachidonic acids eliminate the symptoms but palmitic acid (saturated fatty acid) does not (67).

Investigation also continues on fat emulsions for intravenous feeding of human beings. As purer and purer materials have been used in preparation of these emulsions, most of the reactions have been eliminated. However, even the best emulsions still cause febrile responses in about one-third of the recipients and this effect appears to be related to the speed with which the fat is cleared from the serum, rises in temperature occurring in those persons whose serum is cleared most rapidly (68). There is no evidence that these emulsions induce appreciable hemolysis of erythrocytes *in vivo* (69).

Previous paragraphs in this review indicate the emphasis that investigators of the arteriosclerosis problem have placed on cholesterol levels and the effect of high-fat intake on these levels. Another aspect of this problem, the effect of fats on blood coagulation, has been investigated also. For many years, there have been suggestions that high-fat meals increase the speed

of blood clotting. Fullerton and his associates (70), O'Brien (71, 72, 73), and Maclagan & Bellimovia (74) found a relationship between the ingestion of certain fats, particularly butter, and rapidity of blood clotting as measured by a variety of tests. These investigators were able to show that phospholipides such as phosphatidylethanolamine and phosphatidyl serine rather than chylomicrons were potent clotting process activators. They disagreed, however, on the question of whether margarine and eggs induced this effect. On the other hand, Hall (75) and Tullock (76) were unable to establish any relationship between fats and blood clotting mechanisms. Therefore, this very important investigative field is still clouded with uncertainties.

Protein and Amino Acids

For a number of years, there has been very active investigation on the protein and amino acid requirements of human beings. Definitive evidence concerning these requirements has appeared in the literature in 1955 and 1956. The question of the feasibility and efficacy of supplementation of cereals with deficient essential amino acids has been given serious consideration. The essential amino acids have been given a therapeutic trial in kwashiorkor, a protein-deficiency syndrome of infants and children, and the value of low-protein diets and, in some cases, the amino acids, glutamic acid and arginine has been demonstrated for the treatment of hepatic coma. In the United States where a high and varied protein diet can be obtained easily, these questions are of more academic than practical importance. In terms of global food supply, however, these considerations have great practical significance, for there are many areas where animal protein is consumed only on feast days, a few times each year, and cereal proteins, known to be deficient in several of the essential amino acids, make up the bulk of the protein intake.

Rose and his co-workers have been investigating the amino acids essential for man during the past 20 years. These have been shown to be L-isoleucine, L-leucine, L-lysine, DL-methionine, L-phenylalanine, L-threonine, L-tryptophan, and L-valine. In a series of 38 experiments extending over the past 12 years, they have determined the tentative requirements for these essential amino acids (77). Experimental subjects were healthy male graduate students given a diet consisting of wafers of cornstarch, sucrose, butterfat and corn oil, and inorganic salts (78). This was supplemented with a mixture of vitamins and liver powder. Glycine and urea were added to the mixture of the essential amino acids to increase the total nitrogen intake to 6.7 to 10.1 gm. per day. The caloric content of the diet was maintained at 55 cal./kg./day. This high caloric intake was required since previous work had shown that 25 per cent more calories were required to maintain positive nitrogen balance when amino acids rather than proteins were fed. The tentative minimal amino acid requirement was determined by reducing the level of one of the amino acids stepwise until negative nitrogen

balance occurred. Thereafter, the diet was supplemented with the amino acid until a positive balance was obtained. The highest observed value required to produce barely positive nitrogen balance in all subjects in the test was termed the tentative minimal requirement.

By this technique, the requirement for isoleucine was 0.7 gm. per day (79). Deficiency of isoleucine caused the most negative nitrogen balance observed in these experiments. The requirement was 1.1 gm. when leucine replaced isoleucine. Lysine deficiency (80) caused negative nitrogen balance, loss of appetite, increase in nervous irritability, and fatigue and was prevented by feeding 0.8 gm. of the amino acid daily. An amount of 1.1 gm. of methionine (81) was required in either the D or L forms. L-cystine could replace 80 to 90 per cent of the minimum methionine requirement.

An amount of 1.1 gm. of L or DL-phenylalanine (82) brought about positive nitrogen balance, but the D form alone was ineffective at a 1.5 gm. level, suggesting that about 0.5 gm. of D-phenylalanine could replace the L form. L-tyrosine could replace 70 to 75 per cent of the phenylalanine requirement (83). Threonine (81) was required in doses of 0.5 gm. per day and tryptophan (78) in amounts of 0.25 gm. per day. Valine (77) was effective at a level of 0.8 gm. per day. No requirement was found for arginine, histidine, or other amino acids (84).

The minimum total nitrogen requirement was estimated from experiments on two healthy young men fed twice the minimum requirement of these essential amino acids and supplements of glycine and urea to increase the nitrogen intake to 10 gm. (85). The glycine and urea supplements were gradually decreased during successive 10-day periods and the minimum amount of nitrogen was determined which would maintain positive balance. This was 3.5 gm. per day supplied by 1.42 gm. of nitrogen from essential amino acids, 0.52 gm. from D amino acids which probably were not utilized, 1.21 gm. from glycine, and 0.35 gm. in unknown impurities. This is equal to 21.9 gm. of protein daily. Under these conditions patients gained weight, so these diets must have supported the formation of new protein.

Leverton and associates (86 to 90) have carried out similar experiments on 35 young women. The basic diet used by these investigators provided 35 to 55 cal./kg., all the essential amino acids, plus arginine, histidine, tyrosine, and cystine in amounts equal to those which are found in 20 gm. of egg protein. Additional nitrogen was supplied by glycine and diammonium citrate so that the total nitrogen intake was 6.2 to 9.5 gm. per day. The rest of the diet was composed of cornstarch, sugar, purified butter, corn oil, fruit, carrots, and lettuce. The zone of nitrogen equilibrium was defined as the point at which 95 to 105 per cent of the ingested nitrogen was excreted. The average amount that would bring about this balance in the subjects tested was considered the requirement. This method should give somewhat lower figures than those determined by Rose.

The leucine requirement was .6 gm.; phenylalanine, 0.22 gm. when 0.9 gm. of tyrosine was available; threonine, 0.4 gm.; tryptophan, 0.16 gm., and valine, 0.65 gm.

By use of a similar technique but with a diet which included more nitrogen as cereal protein, Clark and his associates (91) determined the leucine requirement. This was fixed at 0.9 gm. These investigators determined also that large amounts of other essential amino acids had no effect on this requirement.

Swendseid and his associates (92, 93), using a diet containing 7 to 8 gm. of nitrogen in the form of peanut protein, the essential amino acids and glycine, found that the cystine-methionine requirement was 350 to 550 mg. per day. Isoleucine requirement was 250 to 450 mg. per day when the eight essential amino acids were fed at the level of the minimum requirement and the rest of the nitrogen was supplied by glycine; nitrogen balance was maintained for five days of the experiment.

Studies on the threonine and phenylalanine requirements of infants indicate the need for amounts considerably higher per kg. of body weight than those determined by Rose and his associates for adult human beings. The threonine requirement was 60 mg. per kg. of body weight. When no threonine was in the diet, the infants lost weight and developed glossitis and stomatitis. The phenylalanine requirement was 90 mg. per kg. of body weight. No clinical symptoms developed during the short time that phenylalanine was absent from the diets of these infants (94,95). Holt and his associates (96) have determined that the valine requirement of the infant is 85 mg. per kg. of body weight per day. These investigators have evidence that histidine, which is not essential for the adult, is essential for the growing infant. Albanese (97, 98) has found that the requirements of infants for tryptophan, lysine, methionine, and isoleucine are, respectively, 30, 180 to 210, 85, and 90 mg. per kg. of body weight.

Though these data suggest that human beings can exist on very low protein intakes, in the range of 20 gm. per day (approximately the amount found in the rice diet which will support nitrogen balance under controlled conditions), these figures must not be construed to mean this is adequate intake under all conditions. Furthermore, this type of equilibrium can be reached only when the low-protein intake supplies all the amino acids in optimum ratios. Too little or possibly too much of any essential amino acid may upset the equilibrium. This happy state ordinarily can be obtained only by eating a mixed diet containing protein of superior quality. These figures cannot apply to persons doing heavy work under conditions of high temperature or humidity, or who are under special stresses such as pregnancy, lactation, convalescence from an illness or operation, or during a period of growth.

It is probable that these figures apply only to well-nourished persons with adequate labile protein stores. Such stores may exert a sparing action on amino acids necessary for maintaining nitrogen equilibrium (99). Only

for a time will these labile protein stores make possible the adaptation of the body to a poor protein. Therefore, it probably is wise to follow Rose's suggestion that his tentative minimum requirements be doubled if they are used to estimate the needs of human beings for the amino acids.

When considering a protein food as adequate or inadequate, one must consider the amounts of the essential amino acids that it contains, the ratios which they bear to each other, how available they are, how easily digested the protein is, and how easily absorbed the amino acids are (100). Proteins of high nutritive value such as egg and milk properly digested, supply essential amino acids in a pattern remarkably similar to that which the experiments described above have indicated to be optimal for maintenance of nitrogen balance. It is possible, however, by using mixtures of proteins of poor biologic quality, or by using wheat as the principal source, to attain nitrogen balance in adults and good growth in children (101, 102, 103).

Because many areas of the world have insufficient animal protein for the needs of the population which must perforce subsist on low-protein vegetable diets, there has been much interest in the question of supplementation of such low-protein diets with essential amino acids. The work of Hegsted and his associates (104) suggests, from studies on adult subjects, that diets containing 25 gm. of vegetable protein can be improved by the addition of 0.9 gm. lysine and 1 gm. methionine supplements after depletion periods during which diets containing 17 or even 10.6 gm. of protein were fed. These are extremely low protein intakes. Positive nitrogen balance was readily obtained on vegetable diets containing 45 gm. of protein. Albanese (97, 105) has published data supporting the position that malnourished infants consuming a milk diet to which lysine has been added in an amount that will raise the ratio of lysine to tryptophan to 6 (this is the ratio found in muscle and serum), have an advantage in positive nitrogen balance and growth over similar infants who receive no supplement. Other studies do not confirm this position. Since there is evidence from studies in animal nutrition (106) that excesses of essential amino acids which throw ratios out of balance may actually decrease the nutritive value of a protein, a great deal of thought must be given to the problem before pure amino acids are added to foodstuffs destined for human use (107).

Brock (108) and his associates have demonstrated that an essential amino acid mixture will initiate recovery from kwashiorkor. Thirty-three children with this type of severe protein malnutrition were given diets containing purified amino acids with and without vitamin supplements. Diet #1 contained 18 purified amino acids (based on amino acid composition of casein) and diet #2 contained 11 purified amino acids including the eight essential ones. Five of nine children who received diet #1 showed initiation of cure, three had partial response, and one had no response. The addition of a vitamin mixture affected the results very little. With diet #2, the vitamin mixture did make considerable difference. Without

vitamins, none of the seven children improved. With vitamins, diet #2 initiated cure in four, induced partial response in three and no response in one. One child received diet #2 plus glycine to increase the nitrogen content to that furnished by diet #1. Nitrogen retention was much smaller than found when diet #1 was fed, indicating that it is the amino acid pattern rather than the total nitrogen content that is important after a minimum nitrogen requirement has been passed. These data suggest that, as suspected, the major deficiency of the child with kwashiorkor is protein.

Under special circumstances, too much protein may be harmful. Many investigators have demonstrated that patients with chronic liver disease on the verge of hepatic insufficiency may be pushed into hepatic coma by a high protein diet (109). Schwartz and his associates (110) studied three patients who showed clinical improvement in neurologic complications of hepatic insufficiency when the protein intake was curtailed to 40 or 50 gm. daily. These observations must not be construed as indicating that all patients with chronic liver disease should have low protein diets. It has been well established that most patients with chronic liver disease are benefited by high carbohydrate, high protein diets unless they are close to hepatic insufficiency.

High protein diets, methionine, urea, ammonium chloride, and acetazolamide elevate the blood ammonia levels in persons with chronic liver disease. Even though a perfect correlation can not be shown between venous or even arterial blood ammonia levels and hepatic coma, most investigators believe that there is a cause and effect relationship (111, 112). Failure of mechanisms by which tissues deal with ammonia must be responsible for these increases, and it may be that coma is the result of failure of these mechanisms in the brain. α-ketoglutarate, citrate, and lactate are increased in the blood of these patients but the reasons for these increases are in doubt.

On the other hand, sodium glutamate in doses of 24 to 36 gm. intravenously will lower blood ammonia levels and may induce clinical improvement in some patients whose liver function is not too badly impaired (113 to 119). Arginine is said to accomplish these results even more efficiently (120, 121, 122). The dose that has been used is 25 gm. in 500 cc. of 10 per cent glucose. Glutamate can trap ammonia through the formation of glutamine, or by transamination reactions with pyruvate to form alanine and α-ketoglutarate which can accept ammonia. Arginine, by conversion to ornithine, can capture ammonia and ultimately contribute to the synthesis of urea through the ornithine-citrulline cycle (123).

Pantothenic Acid

The pathologic effects of a deficiency of pantothenic acid have not been defined clearly in man. In view of the ubiquitous occurrence of the vitamin in nature, it is unlikely that a deficiency of this vitamin in human subjects will occur except under conditions of most severe deprivation or possibly

in pathologic states which alter the requirements for the vitamin. The "burning feet" syndrome seen in men confined in prisoner-of-war camps in Japan and Burma did not respond to therapy with thiamin, riboflavin, or nicotinic acid and was reported by Gopalon to improve with calcium pantothenate (124). It cannot be concluded, however, that a deficiency of pantothenic acid alone is responsible for this syndrome. Becker and his associates have proposed that a deficiency of pantothenic acid may exist in certain diabetic patients without retinopathy (125). In diabetic patients of this type, the eosinophile response to the administration of ACTH was found to be impaired. After the administration of 100 to 200 mg. of pantothenic acid intramuscularly or 500 to 1000 mg. orally, the eosinophile response to ACTH became normal in 8 of 11 patients. In two patients studied, the 24-hr. urinary oxysteroid excretion was also increased after the administration of pantothenic acid. No defect in acetylation of sulfadiazine was demonstrated. Two patients with pernicious anemia and one patient with sprue were also found to have an abnormal Thorn test, which became normal after pantothenic acid administration. Observations of this type assume importance in view of the extensive experimental work in animals showing a relationship of pantothenic acid to the adrenal cortex and the participation of coenzyme A in steroid synthesis (126 to 129). Recently, it has been demonstrated that alloxan diabetic rats are more susceptible to a deficiency of pantothenic acid than are nondiabetic rats (130).

The clinical and metabolic effects of the administration of a pantothenic acid antagonist, ω-methylpantothenic acid to human volunteers on a pantothenic acid-deficient diet have now been reported by Lubin *et al.* (131) and Bean *et al.* (132). In an initial study on four healthy men, the clinical symptoms and signs that developed during the deficiency period were noteworthy (133, 134). The subjects became quarrelsome, sullen, and petulant. Lethargy and somnolence were evident. Transient numbness and tingling of the hands and feet occurred early. Later paresthesias were a constant source of annoyance. The men frequently stamped their feet and shook or wrung their hands in an effort to restore normal sensation. One subject had an especially disagreeable burning sensation in his feet. All subjects had hyperactive deep tendon reflexes, weakness of the extensor muscles and interossei of the hands, and inability to walk on tip toe. Sensory perception was essentially normal. Vascular instability, postural hypotension, labile pulse or easily provoked tachycardia were prominent. During the deficiency period three men had almost continual upper respiratory infections, particularly acute pharyngitis.

A second group including two normal subjects and a patient with the adrenogenital syndrome were studied in the same fashion and developed similar weakness, fatigue, and decrease in spontaneous activity (131). Dizziness and unsteadiness were severe. Paresthesias were prominent. These subjects did not have much vascular instability, and no tendency to infection occurred.

Metabolic changes include impaired ability to acetylate *para*-aminobenzoic acid, impaired or absent eosinopenic response to ACTH, alterations in carbohydrate metabolism, reduction in blood cholesterol and cholesterol esters, and decreased excretion of urinary 17-ketosteroids.

The data concerning acetylation of PABA are not at all conclusive. In only one subject was acetylation definitely decreased during the deficiency period. In three others, acetylation fell below control values only during periods when the subjects had been restored to normal diets supplemented with pantothenic acid. Three other subjects had no alteration in acetylation during the entire study.

The impaired eosinopenic response to ACTH was more uniform, being present in all but one subject. However, the addition of a normal diet supplemented with pantothenic acid did not restore the normal response in all individuals.

In one subject, glucose tolerance studies showed an elevation in fasting and peak levels of blood sugar during the deficiency period. In two other subjects the 2-hr. blood sugar determination was persistently elevated. All subjects had increased insulin sensitivity which gradually disappeared during the recovery period.

Cholesterol and cholesterol esters fell in all patients during the deficiency period. The addition of pantothenic acid resulted in a greater fall, but the values returned to normal when a nutritious diet was supplied.

In all normal subjects the urinary 17-ketosteroids decreased somewhat during the period of pantothenate deficiency. Following the administration of pantothenate, the 17-ketosteroids remained low or only gradually increased. The patient with the adrenogenital syndrome had a high excretion of 17-ketosteroids during the control period. A definite decrease from these levels was noted during the deficiency period, and persisted after the restoration of a nutritious diet supplemented with pantothenic acid.

In three subjects studied alterations in serum potassium and chloride occurred. Extreme degrees of hypochloremic alkalosis and hypokalemia developed in two subjects during the deficiency period and were restored to normal only by a normal diet supplemented with pantothenate. In the third subject mild changes in this direction occurred.

Careful observations on gastric secretion and motility were made (135). No change in gastric motility was noted during the deficiency state. Two of three subjects developed severe depression of gastric secretion. Pepsin secretion in response to insulin and histamine was also diminished. It was postulated that the parietal cells were depleted of an essential metabolic factor, possibly coenzyme A. On the other hand, the diminished secretion may have been an indirect expression of adrenal cortical hypofunction.

Bean and his associates have pointed out that their observations are preliminary, and the conclusion that pure uncomplicated pantothenate deficiency alone accounts for the observed changes is not justified. Whether ω-methylpantothenic acid is a more powerful toxic agent working as a

general protoplasmic poison or whether some unrecognized deficiency exists in the experimental diet must also be considered. The failure of pantothenic acid to reverse completely the abnormalities noted does not seem necessarily incompatible with a deficiency state. An analogy exists in the deficiency of folic acid induced by folic acid antagonists. The signs are difficult to reverse with folic acid and are relatively easily reversed with folinic acid. Perhaps in the present case pantotheine or coenzyme A might be more effective (131).

Although it is tempting to explain many of the changes during the deficiency period to suppression of adrenal cortical function, the paradoxical finding of hyperglycemia associated with increased insulin sensitivity as well as the hypokalemic alkalosis raises some intriguing problems. It must be said that a definitive answer to the above problems is not now available.

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ENDOCRINOLOGY[1,2]

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Progress in endocrinology has been rapid. So large is the field that in one year's harvest an entire chapter could be devoted to each of the endocrine glands. Remarkable achievements have been in many instances because of the successful application of newer techniques such as chromatography, radioisotope tracer procedures, and microchemical analyses. In this review an appraisal has been made of experimental work relating to the anterior pituitary, thyroid, adrenal cortex, parathyroid, and pancreas.

Anterior Pituitary

Much interest has been shown in the hormones of the anterior pituitary. Variability of experimental data pertaining to these hormones has resulted, in large measure, from the use of impure preparations and, although improved methods of purification have become available, they remain expensive and laborious. Highly purified hormones are now obtainable for research purposes from the Endocrinology Section of the National Institutes of Health (1), and it seems likely that their use will lead to a better appraisal of the specific action of these substances.

For many years attempts have been made to ascribe specific hormonal functions to the various cells of the pituitary. At first there was only conjecture, but later assignation of function to specific cell types was based on histological examination of the pituitary in patients with various glandular disorders. More recently, special stains and solvents, bioassays, and selective destruction of minute parts of the pituitary have been applied to this analysis. Many such studies have been performed and the definitive results of a recent project are outlined by Barrnett *et al.* (2). These workers show that thyrotropic, follicle-stimulating, and luteinizing hormones are localized to those basophiles which have an affinity for periodic acid-Schiff stain.

Growth hormone (GH).—It has been recognized that growth hormone from bovine or porcine sources is ineffective in man. Indeed, a degree of

[1] The survey of literature pertaining to this review was completed in August, 1957. For the sake of brevity the abbreviation *et al.* is used when three or more authors' names appear on a paper.

[2] The following abbreviations are used: GH (growth hormone); ACTH (adrenocorticotropin); MSH (melanocyte-stimulating hormone); TSH (thyroid-stimulating hormone); FSH (follicle-stimulating hormone); LH (luteinizing hormone); PBI (protein-bound iodine); BMR (basal metabolic rate); TBP (thyroxine-binding protein); PTH (parathyroid hormone); GFR (glomerular filtration rate); Tm_P (maximal rate of tubular reabsorption of phosphorus by kidney); Tm_G (maximal rate of tubular reabsorption of glucose by kidney).

species-specific effects has been shown for GH extracted from the pituitaries of fish, rats, monkeys, and man. For example, nitrogen retention in the hypophysectomized monkey can be achieved by administration of purified monkey GH, but not from bovine GH (3). Preparations of GH from animals do not alter nitrogen balance or glucose tolerance in man; they have been shown, however, to decrease the rate of formation of plasma phospholipide, an effect which may correspond to the abnormality which has been observed in acromegalics (4). Li (5) has postulated that the differences in metabolic properties of GH obtained from various species are due to variations in molecular structure of the hormone specific for each species. More recently, in support of this, Li & Papkoff (6) have shown that bovine GH has a molecular weight of 46,000, whereas human and simian preparations have a weight of approximately 26,000. Differences in amino acid content were shown as well as in the pH of the isoelectric points.

Preparations of GH, isolated from human beings and monkeys in high purity by Raben (7), were similar in producing weight gain and retention of nitrogen, phosphorus, calcium, and sodium in a patient with hypopituitarism (8). The simian preparation, however, also produced oliguria, a reaction not observed with human GH in doses of 10 mg. daily.

Prudden *et al.* (9) have shown that in four severely burned patients GH promoted increased retention of nitrogen during anabolism, whereas during the catabolic phase of injury the hormone accelerated nitrogen loss. They suggested that GH requires the presence of other endocrine factors in order to secure effective anabolism. That GH may not induce "growth" as its name implies, but may act synergistically with or as an accelerator of other hormones has also been postulated by Li (10).

The mechanism by which GH induces diabetes remains unanswered. In rats made diabetic by partial pancreatectomy or alloxan, the administration of GH produces only transient exacerbation of glycosuria followed by diminished glycosuria, often to a degree less than that in the preinjection period; and the pancreatic islet cells appear larger and healthier as a result of GH administration (11). The normal rat given GH also develops diabetes transiently if the dietary intake of carbohydrate is large (12). Such observations suggest that the secretion of insulin is implicated in the hyperglycemic action of GH. Houssay & Penhos (13) have continued studies initiated by Houssay many years ago on the relationship of the pituitary hormones to diabetes mellitus. In dogs which have been partially pancreatectomized and totally hypophysectomized and adrenalectomized, the administration of either GH or prolactin induces diabetes. In these animals ACTH does not produce overt diabetes but, as might be expected, cortisone shortly produces hyperglycemia.

A refined method of bioassay of GH has been developed by Lostroh & Li (14). In hypophysectomized mice GH in amounts as small as 0.001 mg. daily is detected by noting the extent of the increase of width of the epiphyseal cartilage of the tibia. By employing the synergistic effect of thyroxine

the assay can be shortened in time. The content of GH of the adult human pituitary has been shown to be from 3.7 to 6.0 mg. (15).

In rats the anemia induced by hypophysectomy is not corrected by the administration of GH, although GH appeared to induce bone marrow proliferation (16); since the preparation used was secured from Armour and Company, the GH was probably bovine or porcine.

Renal function in a patient with gigantism and acromegaly has been evaluated by Gershberg *et al.* (17). Glomerular filtration rate and activity of the proximal tubules as measured by various clearance techniques were increased. The kidneys, when later examined at autopsy, were huge as were the glomeruli and tubules on microscopic examination; the "growth" of the kidneys readily accounted for the findings in renal function observed during life.

Adrenocorticotropin (ACTH).—Li & Dixon (18) have reported the isolation and properties of bovine ACTH. This exacting work elucidates the amino acid content of ACTH as well as the structural sequence of some of its amino acids. The preparation appears identical to α-corticoptropin isolated from sheep pituitary. The content of ACTH of the rat pituitary has been assayed by Birmingham *et al.* (19); by extraction with glacial acetic acid the content of ACTH was found to be 1.3 units per gland, an amount much greater than that found by earlier techniques in which dilute hydrochloric acid was used as the extractant. Brodish & Long (20), employing a delicate but accurate cross-circulation technique to assay ACTH, have shown that in the rat following severe stress the pituitary secretes ACTH at a high rate about 2 hr. and then the secretion diminishes to nothing within 6 hr. With mild stress the increased rate of secretion is less marked but continues for at least 12 hr. The absence of ACTH in the blood 6 hr. after severe stress was not attributed to pituitary suppression by adrenal hormones, since this occurs also in adrenalectomized rats. A second severe stress produces a fresh elaboration of ACTH, showing also that the pituitary's supply of ACTH is not exhausted. Methods of measurement of ACTH in human beings have been refined; Persky & Heath (21) have found a uniform response in the plasma hydrocortisone level following ACTH administration in normal subjects, and the data allow for the calculation of ACTH values. Of the two repository forms of ACTH, gel-ACTH and Zn-ACTH, the latter has a more marked effect on the level of plasma 17-hydroxycorticosteroids at 8 hr. after administration, although at 2 hr. the two were equally potent in producing a 2.3-fold rise above pretreatment levels (22). Christy *et al.* (23) found prednisone four times as effective as cortisone in suppressing the effect of ACTH on the adrenal cortex.

Guillemin and his associates (24) have isolated from hypothalamic tissue a substance, probably a complex polypeptide, which stimulates the release of ACTH from the rat pituitary. The results of these experiments support previous works which indicate that ACTH secretion is, at least in part, affected by hypothalamic mechanisms. That these mechanisms can be blocked

is shown by the fact that reserpine, if administered daily for several days, prevents ACTH discharge during stressful stimuli, presumably by suppressing the hypothalamus (25). On the other hand, single doses of reserpine, as well as chlorpromazine, result in marked discharge of ACTH (25, 26, 27). Bogdanove (28) has indicated that there may be separate hypothalamic-hypophyseal pathways or mechanisms responsible for stimulating production of thyrotropin, gonadotropin, and adrenocorticotropin. McCann (29), searching for the neurohumoral agent responsible for ACTH release, has presented evidence that the antidiuretic hormone is responsible for such an effect. Amphetamine has an ACTH-like action, since it induces a rise in the level of plasma 17-hydroxycorticosteroids (30).

The significance of pituitary basophilism has been summarized by Kovacs *et al.* (31). Excess numbers of basophil cells appear in the pituitary upon the administration of cortisone (32). Purves (33) and Crooke (34) hold that this results not from diminished ACTH secretion but from increased production of follicle-stimulating hormone, and indeed Kovacs *et al.* (31) have found such an increase. Nonetheless, pituitary basophilism appears only in the presence of an excess of the corticosteroids. Large doses of corticosteroids alter the morphological appearance of the anterior pituitary (35). In patients with leukemia who received more than 27 gm. of prednisolone in the few days prior to death, there was a diminution of basophilic cells not staining with periodic acid-Schiff reagent and increased staining of the remaining basophiles; the latter were considered likely to be thyrotropic cells.

At least three deaths from allergic reactions have been reported during therapy with ACTH (36). Impurities in the preparations of ACTH now available could partly account for these reactions, and Dixon *et al.* (37) have called for higher purification. Mom (38) has found that staphylococcal skin infections, resistant to antibiotics, often respond to treatment with ACTH. Doses of 20 to 80 units daily for only a few days were required. Although several investigators have previously reported that ACTH and cortisone produce changes in the electroencephalogram, Friedman & Engel (39) have detected no change in the patterns of normal subjects given moderate amounts of either ACTH or cortisone daily for six days.

An important contribution to our knowledge concerning the production of obesity by pituitary tumors has been made by Mayer *et al.* (40). A transplantable tumor of unique type induces in recipient mice adrenal hypertrophy, atrophy of lymphoid organs, lymphocytopenia, and obesity. The remarkable feature resulting from this tumor, however, is the great increase in the content of fat and cholesterol in liver and carcass. This obesity may occur at the expense of other tissue substances, since excess fat remains even if weight reduction is induced by diet restriction. This type of obesity stands in contrast to that produced by hyperphagia in which there is no reduction of other tissue substance even in the presence of marked obesity.

A concise review of the relationships between melanocyte-stimulating hormone (MSH) and ACTH appears in the *British Medical Journal* (41). Both ACTH and MSH are polypeptides. The former, however, has 39 amino acids in a single chain, while the latter has only 18. The sequence of seven of the amino acids is common to both. As with GH and other protein-type hormones, specificity in chemical structure of MSH and ACTH may exist in each species. High levels of MSH and ACTH are found in patients with Addison's disease; both decrease during treatment with cortisone. The suggestion is made that there may be evolutionary, as well as clinical, relationships between MSH and ACTH.

Thyrotropin (TSH).—Two new assay procedures for TSH have appeared. One is based on the TSH-induced depletion of radioiodine from the thyroid gland of day-old chicks (42). The other relies on the effect of TSH in accelerating radiophosphorus incorporation into the lipide fraction of thyroid slices (43). These techniques, the former *in vivo* and the latter *in vitro,* have a similar high index of precision. Levey & Solomon (44), in studying the metabolism of TSH, have shown that exogenous TSH disappears rapidly within 1 hr. from plasma and that the thyroid gland and liver appear unimportant in the inactivation of administered TSH. Urinary excretion of TSH was minor. The mechanisms and sites responsible for inactivation of TSH remain unknown. Alpers & Rall (45) have shown that TSH *in vitro* does not promote proteolysis of thyroglobulin. Thyrotropin has been observed to inhibit strongly the coagulation of milk by pepsin (46).

The relationship between the production of TSH by the pituitary and the production of thyroid hormone by the thyroid gland has long been thought to be controlled by a "feedback" mechanism; that is, in response to diminished or increased circulating thyroid hormone, the pituitary alters production of TSH in order to maintain homeostasis. That the homeostatic mechanism may be more complicated than this is established by the experimental work in animals of Goldberg *et al.* (47). Dinitrophenol prevents thyroid hyperplasia induced by propylthiouracil and at the same time inhibits the appearance of changes in pituitary cells indicative of excess TSH excretion. Since, in addition, dinitrophenol accelerates metabolism, these workers postulate that some product of the metabolic action of cells, rather than the level of thyroid hormone in the blood, is the factor controlling output of TSH by the pituitary. A definitive study showing the quantitative relationships of TSH secretion to thyroxine production during metamorphosis of the toad *Xenopus laevis* has been carried out by Saxen and his co-workers (48).

The pharmacologic inhibition of pituitary hormones has been investigated by Sonenberg & Money (49). Acetylation of TSH with acetic anhydride results in a preparation lacking specific "tropic" effects on the thyroid; on the other hand, the preparation prevented the "tropic" effects of unmodified TSH. Thus, acetylated TSH appears to have an affinity for

thyroid tissue while possessing no metabolic properties other than to render the thyroid unsusceptible to the effects of TSH. Sonenberg *et al.* (50) have administered acetylated TSH to a few patients with thyroid cancer or hyperthyroidism with encouraging results.

Gonadotropins.—An improved method of assay for urinary gonadotropins has been developed by Loraine & Brown (51). The reference standard was gonadotropin isolated from the urine of menopausal women. Extracting sufficient gonadtropin from the urine of men and of women in the menstrual phase of life requires large volumes of urine and often results in preparations toxic to the test animals; these authors report a purification procedure obviating this difficulty. The gonadotropic activity of urine from menopausal women was five times that of men and 20 times that of normally menstruating women. Brown (52) has detected qualitative differences in human urinary gonadotropins and points out that assays in animals of different strains may yield divergent results. Rothchild (53) has shown that large doses of progesterone (100 to 400 mg.) given intravenously daily to women resulted in diminution of excretion of urinary gonadotropin in five of six menopausal subjects and insignificant decreases in two nonmenopausal subjects. The gonadotropin content of the pituitary of pregnant and pseudopregnant rats does not appear to be reduced by the abortifacient, ergotoxine (54).

Further studies to differentiate those cells of the anterior pituitary which secrete follicle-stimulating hormone (FSH) from those which secrete luteinizing hormone (LH) have been done by Griesbach *et al.* (55). The induction in male rats of vitamin E deficiency, long known to produce testicular degeneration, at first causes damage to the tubules of the testes with secondary hypertrophic changes in those cells of the pituitary thought to produce FSH. Later, slight hyperplasia of the testicular interstitial cells occurs; and the so-called LH cells of the pituitary become hyperplastic. The FSH cells appear to be in the peripheral portion of the anterior pituitary, whereas LH cells are central, although Rennels *et al.* (56) are said to ascribe reverse positions to the gonadotropin-producing pituitary cells.

The preparation of highly purified porcine FSH has been accomplished by Steelman *et al.* (57). This material has a molecular weight of approximately 29,000 and contains about 7 per cent cysteine. Dosage of 0.001 to 0.0025 mg. increases the weight of ovaries of immature hypophysectomized female rats.

Pituitary gonadotropins obtained from spawning salmon induced sexual maturation in male trout (58). In the male frog FSH increased the number of primary spermatogonia of the testes, and LH stimulated interstitial cells and released sperms into the lumen of the tubules (59).

An improvement in a test for pregnancy has been developed by Hon & Morris (60); the toad *Bufo marinus,* which is always available, is injected with a condensation of a 12-hr. urine sample which has been partially purified by adsorption on kaolin and alumina at controlled pH. In the pres-

ence of chorionic gonadotropins the toad responds by elaborating sperm. The test is of value not only in establishing the existence of pregnancy, but also in detecting abnormal pregnancy with low levels of excretion of gonadotropins and high levels associated with choriocarcinoma. Chorionic gonadotropin is reported to be effective in the treatment of migraine; hirsutism developed in one patient (61).

Autotransplants of ovarian tissue to spleen result in tumors of the transplant, probably because of stimulation of the ovary by excess gonadotropins. Ely (62) has shown that the administration of antigonadotropic serum to mice bearing ovarian transplants effectively reduces the incidence of tumorogenesis of such transplants. In like manner, he has shown (63) that antigonadotropic serum effectively inhibits the ovarian changes which occur secondarily to x-ray irradiation. Thus, antigonadotropic serum appears to block effectively the stimulatory properties of gonadotropin on ovarian tissue.

Prolactin (Mammotropin).—Segaloff and his associates (64) have shown that prolactin, obtained from porcine, ovine, or bovine sources, sensitizes the ventral prostate gland of the hypophysectomized rat to the luteinizing hormone. Bahn & Bates (65) have been unable to measure pituitary production of prolactin from the serum or urine of human beings. The work of Furth and his associates on prolactin-producing tumors of the pituitary has been summarized (66). Studies of the actions of this tumor will aid, as Hadfield (67) has indicated, in the elucidation of hormone dependence in breast cancer.

Hypophysectomy and hypopituitarism.—Additional reports during the past year have been forthcoming concerning the beneficial effects of hypophysectomy in women with extensive cancer of the breast. Kennedy *et al.* (68) noted improvement in 18 of 21 patients treated in this manner. Olivecrona and his associates (69, 70, 71), whose experience is now extensive, noted improvement in 22 (54 per cent) in their series of 41 patients. Andersson (72) achieved improvement for nine of his 20 patients. Lebeau and his associates (73) have operated on 25 patients and believe that the operation is contraindicated in patients with liver metastases. A study to determine if hypophysectomy is better than adrenalectomy with oophorectomy has been conducted by Atkins and his co-workers (74); the former procedure appeared somewhat better than the latter, although the results, comprising 30 patients in each series, were not statistically significant. The results of most investigators indicate that approximately half of the patients undergoing hypophysectomy for breast cancer show temporary retardation of cancer growth; and, indeed, regression of tumor occurs in some. Subjective improvement is noted in many patients who clinically are not benefited. The procedure, then, is often palliative, never curative. Such studies have also furnished valuable incidental information as to the rate of appearance of deficiency states resulting from failure of the pituitary's target organs and the efficacy of successful replacement therapy. Allen

et al. (75) note that the patients who derive the greatest benefit from either hypophysectomy or adrenalectomy with oophorectomy seem to be those who preoperatively show greater excretion of the 11-deoxy-17-ketosteroids as compared to the 11-oxy- or 11-hydroxylated-17-ketosteroids. The former represent excretory products of testosterone and its closely related compounds, the latter of cortisone and its related substances.

Hypophysectomy has been done also for carcinoma of the prostate, malignant melanoma, chorioepithelioma, carcinoma of the thyroid, malignant exophthalmos, and diabetes mellitus with Kimmelstiel-Wilson's disease (76).

Destruction of the hypophysis has been accomplished by implantations of radioactive gold or yttrium into the pituitary by means of a cannula inserted through the nose (77). Although complete ablation of the pituitary was not achieved, the chromophobe, eosinophil, and basophil cells appeared to be equally susceptible to the damaging effects of the radiation.

An investigation of sodium chloride balance following hypophysectomy in nine patients with breast cancer has been conducted by Maclean *et al.* (78). The response of these patients to a low salt diet was met by conservation of salt by means of a sharp reduction in urinary sodium chloride excretion. In such patients hyponatremia occurs only if the fluid intake is excessive in the presence of a low salt intake. Aldosterone appears normally abundant. These investigators (79) also compared the response of hypophysectomized and adrenalectomized patients to the withdrawal of cortisone. The hypophysectomized patients tolerate such a condition better than the adrenalectomized. The existence of aldosterone secretion or the presence of diabetes insipidus in the hypophysectomized patients was not thought to account for this difference. Munro (80) observed marked fluctuations in the total exchangeable sodium and serum sodium values in a patient with severe panhypopituitarism. The values varied from low to normal. With cortisone therapy, however, the patient improved; and these values became consistently normal.

The activity of the reticuloendothelial system is, at least in part, under hormonal control (81). In hypophysectomized rats the spleen accepts radioactive gold particles in greater amounts than in intact rats. During replacement therapy with GH, ACTH, or hydroxycorticosterone the affinity of the spleen for such particles decreases toward normal.

In rats, hypophysectomy is followed by a reduction in the weight and amylase content of the parotid glands (82). Similarly, there is a reduction in the weight and tubular atrophy of the submaxillary glands with a loss of enzymatic activity; this process is corrected by the simultaneous administration of testosterone and thyroxine (83, 84). Ganong & Hume (85), investigating the effect of partial hypophysectomy in dogs, have shown, as is known also to occur in man, that gonadal atrophy occurs with subtotal (75 per cent) removal of the pituitary and that with more complete (75 to 95 per cent) removal atrophy of the thyroid also occurs and with near

complete (97 to 99 per cent) ablation atrophy of the adrenals appears. Moreover, even in the presence of an atrophic adrenal, the gland responds to stressful stimulus with an outpouring of corticoid provided that a pituitary remnant is present.

Selye *et al.* (86) produced nephrocalcinosis in rats by the administration of sodium phosphates; nephrocalcinosis does not develop, however, in hypophysectomized rats. Ventura & Selye (87) also show that hypophysectomy abolishes the lytic effect of deoxycorticosterone acetate on the spleen and thymus of either adrenal-intact or adrenalectomized rats. The mechanism of the protective effect of hypophysectomy in both experiments is unknown.

Tumors.—It has been long recognized that tumors of the pituitary do not metastasize widely, although occasionally they show local extension. The invasive properties of pituitary tumors have been studied by Jefferson (88) and reviewed in the *British Medical Journal* (89). These tumors often fail to attach themselves and grow even when their cells are transported to distant sites by the spinal fluid. This phenomenon is of considerable interest and deserves additional examination.

Mogensen (90) details the results of surgical removal of chromophobe adenoma in 60 patients. Seven patients died as a result of the operation. Ten patients received x-ray therapy postoperatively because of the extent of the tumor growth or the highly malignant appearance of the tumor microscopically. Seven patients suffered recurrence of the tumor; two of these died. Various degrees of hypopituitarism resulted postoperatively. Only one patient developed diabetes insipidus. Hormonal replacement was effectual. According to Mayr *et al.* (91), chromophobe tumors have been found to occur more frequently in persons of group O blood type and less frequently in persons of group A. The incidence of group O blood type among the populace of Boston is 45.8 per cent, whereas over 60 per cent of 123 patients with chromophobe tumor (admitted to one of several Boston or New York hospitals) were group O. On the other hand, 39.7 per cent of the populace is group A, and only 19.5 per cent of the patients were group A. No striking variation in incidence of the tumor was noted in individuals of group B or AB types.

Miscellaneous.—Skeletal deformities and aortic aneurysms in rats result from the feeding of the sweet-pea, *Lathyrus odoratus*. The condition, known as lathyrism, can also be induced by the parenteral administration of β-aminoacetonitrile. Selye & Bois (92) have shown that concomitant administration of somatotropic hormone with aminoacetonitrile induces extremely marked excess proliferation of the periosteal bones and cartilage.

Extensive endocrinological examination of nine patients with anorexia nervosa was accomplished by Emanuel (93). All showed diminished function of the anterior pituitary, thyroid, adrenal cortex, and ovary, whereas in two additional patients who had recovered from this disability endocrine function was normal.

The first report of the Laurence-Moon-Biedl syndrome in an Arab has

appeared (94). The 13-year-old lad had obesity, infantile genitalia, mental retardation, retinitis pigmentosa, and polydactylism.

Thyroid

In his presidential address before the American Goiter Association in 1956, Rawson (95) delineated the advances in thyroid physiology of the last decade and indicated many questions which remain unanswered. The large number of publications pertaining to the thyroid which have appeared during the past year attest to the eagerness with which the answers to these questions are being sought.

Tests of thyroid function.—Oliner and his co-workers (96) have reassessed the radioiodine tracer test in children and find that the values for the 24-hr. uptake in hyper- and hypothyroid patients, as well as in euthyroid subjects, correlate well with the usual ranges for adults. On the other hand, the incorporation of the radioiodine into thyroid hormone, as determined by measurement of the level of serum protein-bound iodine^{131}, was increased in euthyroid children from one to four years of age and was "high normal" to the age of nine years. Thus, there appears to be relative thyroidal hyperactivity in normal infants and children.

Appraisals of the thyroid "battery" of tests have been reported. Fraser (97) concluded that radioiodine tracer tests are superior in the diagnosis of suspected thyrotoxicosis, whereas the protein-bound iodine (PBI) level was more accurate in cases of minimal hypothyroidism. Perloff (98) found the radioiodine tracer test 90 per cent accurate in the diagnosis of thyrotoxicosis and somewhat less valuable in indicating hypothyroidism. The PBI was slightly less accurate, but the two tests combined were diagnostic in 85 per cent of the cases studied. Skanse *et al.* (99) found that in the evaluation of borderline hypermetabolic subjects, the radioiodine tracer test was the most valuable single test.

McConahey and his associates (100) have appraised seven parameters of radioiodine testing and find that the most accurate test is the 6-hr. radioiodine uptake, which also is more convenient than the 24-hr. uptake. The tests are best in exophthalmic goiter, less accurate in toxic nodules, and of least value in myxedema. Other variations in technique of radioiodine testing have been described (101, 102); and again, early measurement of uptake was found to be superior to the 24-hr. uptake. DeAmicis & Williamson (103) have shown that there is no significant difference between results obtained with the scintillation counter and those with a Geiger-Muller four-tube device, although each has certain advantages over the other. Several drugs interfere with thyroidal uptake of radioiodine. Roche & Layrisse (104) have shown that cobaltous chloride reduced the 24-hr. uptake in 12 adults to almost zero; and Kriss *et al.* (105) have reported that cobalt exerts a direct effect on the thyroid cell, causing increased phosphorus uptake. Slingerland (106) finds that iodoalphionic acid (Priodax) lowers the I^{131} uptake in euthyroid individuals for about one month, although in hyper-

thyroid subjects its depressant effects persist for only one week. Newman & Cupp (107) confirm these findings in euthyroid subjects and add that, although TSH temporarily overcomes the suppression, it does not shorten the over-all period of effect of iodoalphionic acid. Butazolidine also has been shown to depress thyroidal radioiodine uptake, but this effect seems to be transitory (108).

Margolese & Golub (109) have found cyclic variations within a 1.5 μg. per cent range in the PBI level of human subjects over a period of one month. A comprehensive list of drugs spuriously increasing PBI values has been published (110). Keitel & Sherer (111) have demonstrated that testosterone therapy produces a sharp drop in serum PBI levels to the hypothyroid range without the development in the subjects of clinical manifestations of hypothyroidism. The best explanation for the finding seems to be a reduction in the thyroxine-binding capacity of the plasma. Higher PBI values are noted in patients with obstructive jaundice than in those with parenchymal liver dysfunction (112). Hydovitz (113) has found no detectable change in plasma PBI^{131} as a result of anesthesia or thyroid surgery and considers it unlikely that thyroid storm occurs on the basis of extrusion of hormone into the blood during these procedures.

The response of the thyroid to TSH has been used as a test of thyroid function (114). Skillern *et al.* (115) concluded (*a*) that a normal response to TSH rules out primary thyroid failure; (*b*) that a normal test rules out primary hypothyroidism in a patient on thyroid therapy; (*c*) that the test is of value in differentiating Hashimoto's disease from nontoxic nodular goiter; and (*d*) that the test may be helpful in the differential diagnosis of exophthalmos.

Several new tests and modifications of old tests have been reported. Hamolsky *et al.* (116) have found a high degree of correlation between the *in vitro* uptake of I^{131}-labelled triiodothyronine by erythrocytes and the clinical status. Slade (117) has described a simplified ion exchange resin technique for determination of serum PBI^{127} or PBI^{131}. Werner (118) has reported persistence of hyperactivity in the thyroid remnants of some euthyroid subjects who had had successful surgery or I^{131} therapy for hyperthyroidism many years previously. This finding may be of prognostic, as well as diagnostic, value in determining which patients might develop recurrent hyperthyroidism. Perloff *et al.* (119) have also studied the activity of thyroid remnants.

Hamlin & Vickers (120) report their experience with needle biopsies of the thyroid gland. They conclude that the procedure is warranted only when the possibility of thyroiditis is present, since this finding would obviate surgery. Lindskog & Goldenberg (121) have reviewed factors of importance in establishing the diagnosis and treatment of substernal goiter. Gabrielsen & Kretchmar (122) note no correlation of the ratio of salivary secretion of I^{131} to plasma nonprecipitable I^{131} with the thyroid status. Several authors (97, 98, 123) point out that the basal metabolic rate (BMR) is still useful

as an index of the severity of thyrotoxicosis, while other authors (124, 125, 126, 127) report on additional aspects of the BMR.

Hyperthyroidism.—The etiology of hyperthyroidism continues to be the subject of much investigation (128, 129). Lewis & Macgregor (130) have reported a newborn infant with congenital hyperthyroidism whose mother was thyrotoxic during pregnancy, as has been noted in other instances of this condition. The mechanism seems to result from the transplacental passage of maternal TSH. The resulting hyperthyroidism in the infant is normally self-limiting and iodine is usually the treatment of choice (131), although Lewis & Macgregor's case required carbimazole; Kempton & Ratcliff (132) have reported a thyrotoxic infant given only supportive treatment, and evidence of hyperthyroidism disappeared in four weeks.

Harris & Woods (128) have found differences in thyroid function before and after adrenalectomy following electrical stimulation of the hypothalamus or tuber cinereum, and suggest that psychic stimuli cause decreased adrenal activity with resultant increase in thyroid activity in persons with Graves' disease, whereas in euthyroid subjects the reverse occurs. It has been suggested (129) that psychic stress is one cause of unsatisfactory response of some thyrotoxic patients to somatic treatment. Adams & Purves (133) hold that hyperthyroidism is best explained by the presence in the serum of a circulating thyroid stimulator similar to TSH, but not suppressed by excess thyroid hormone. Reichlin (134) has published data which agree with the earlier work of Greer (135) showing that there may be two kinds of TSH, one affecting the iodide trap of the thyroid and the other stimulating the growth of the follicle cells and release of hormone. Bogdanove & Bogdanove (136) have shown, however, that the dichotomy of TSH action which led Greer to postulate two kinds of TSH was due to dosage factors; the thyroidal iodide trap is more sensitive to TSH than is hyperplasia of thyroid cells or release of hormone from the gland. D'Angelo & Traum (137) find that lesions of the hypothalamus can inhibit goiter formation in rats on propylthiouracil. Moreover, the rat pituitary produces TSH even in the absence of the anterior hypothalamus.

Evidence continues to accumulate implicating the pituitary as the cause of exophthalmos in Graves' disease (133, 138), although both triiodothyronine and thyroxine have been shown to produce exophthalmos in the fundulus (139). The treatment of exophthalmos has been extensively reviewed (138, 140, 141). Although some points are controversial, there is general agreement that the nonsurgical approaches, cortisone, desiccated thyroid, and radiation of orbit or pituitary, have not been consistently effective, although they are worthy of trial. Surgical treatment should be administered before irreparable damage to the eyes has developed; lateral decompression of the orbit is the most effective surgical procedure for severe exophthalmos.

The dangers of new drugs in the treatment of hyperthyroidism have been reviewed (142). Experience with carbimazole has been reported by several authors (143, 144, 145) who agree that it is effective and probably less toxic

than other antithyroid drugs, with the possible exception of perchlorate. The use of thiouracil drugs in the treatment of childhood thyrotoxicosis has also been reviewed (146). McCullagh (147) has summarized factors of importance in selecting the proper method of treatment for thyrotoxicosis.

Experience with the use of radioiodine in the treatment of hyperthyroidism is becoming world-wide (148, 149). Estimation of the effective therapeutic dose of radioiodine is the most difficult aspect of this type of therapy. Macgregor (150), reporting good results, simply selects a dose based on the estimated size of gland, whereas Bauer & Blahd (151) recommend a more elaborate and quantitative means of dosage determination. Werner (152) has pointed out the need for knowledge concerning the frequency of exophthalmos following I^{131} therapy for thyrotoxicosis as compared to surgery, and has also indicated the lack of knowledge of the long-term effects of the radiation.

Surgery of the thyroid gland has been reviewed by Rienhoff (153). Beahrs *et al.* (154) report a 0.1 per cent mortality rate in all thyroid surgery at the Mayo Clinic between 1945 and 1955. Vocal cord paralysis and tetany account for the majority of the postoperative complications, with incidences of permanent recurrent laryngeal nerve damage of 1.3 per cent and of permanent postoperative hypoparathyroidism of 0.2 per cent. Piercy & Lange (155) have considered the problem of recurrent goiter following surgery and believe that the reason for most recurrences was removal of insufficient thyroid tissue. They advocate in particular ligation of the inferior thyroid arteries and removal of the pyramidal lobe.

Spjut and his co-workers (156) find no evidence in a clinical study that thyroid hyperplasia leads to eventual struma lymphomatosa. Extrathyroidal hyperthyroidism (157), the association of thyrotoxicosis with acromegaly (158), and the occasional occurrence of hypersplenism with thyrotoxicosis (159) have been reported. The co-existence of thyrotoxicosis and myocardial infarction has been reviewed (160).

Hypothyroidism.—Stanbury & Querido (161) have recently reviewed and classified the various types of cretinism. Endemic goiter with cretinism has been reaffirmed as deriving from iodine deficiency (162), although Costa (163) has presented objections to this theory in certain cases. Much interest has been stirred in sporadic goitrous cretinism, and numerous reports on this condition have appeared (164 to 171). It is now generally accepted that these patients have defective synthesis of thyroid hormone. Stanbury *et al.* (172) have reported three cases having a defect in dehalogenation of mono- and diiodotyrosine, causing these thyroxine precursors to appear in the blood stream. Werner *et al.* (165) have investigated a patient in whom there was a failure of coupling of the iodotyrosines. Schultz *et al.* (166) have studied a goitrous cretin in whom there was failure of organification of iodine, although trapping of iodine by the thyroid gland was normal. DiGeorge & Paschkis (164) have observed a patient with an abnormal iodinated compound in the peripheral blood which may be non-

proteolized thyroglobulin. McGirr and co-workers (168) have reported additional cases of failure of dehalogenation and have further clarified the disorder by showing that this specific defect is due to the absence of a single autosomal recessive gene.

Logan (173) has reported two cases of xeroderma pigmentosa with cretinism; these patients have an increased thyroidal radioiodine uptake which diminishes to normal after treatment with vitamin A. Thyroidal function in mongolism has been studied, and although one group (174) finds no evidence of thyroid abnormality, another (175) finds a significantly faster thyroidal iodine turnover.

The effects of iodine administration on the euthyroid gland have been reviewed and cases are reported of goiter formation and hypothyroidism resulting from prolonged iodide administration (176 to 179). The mechanism is presumably hyperplasia secondary to prolonged block of thyroid hormone synthesis by the iodine. Sodium iodide has been shown to suppress thyroidal activity by local action on the thyroid gland rather than by TSH inactivation (180).

More has appeared in the literature concerning the syndrome of metabolic insufficiency and its successful treatment with triiodothyronine (181, 182). It has, however, been pointed out that a clear and rigorously controlled demonstration of the effectiveness of this treatemnt is lacking; and therefore at present the validity of the observations must be held in question (183, 184). Jefferies *et al.* (185) have shown the existence of a state of low thyroid reserve, manifested by normal radioiodine uptake and PBI level but with failure of the thyroid to respond to exogenously administered TSH. Some of these patients have symptoms of mild hypothyroidism which can be corrected by desiccated thyroid administration.

Triiodothyronine has again been shown to be the treatment of choice in myxedema coma (186, 187, 188), although warnings against using even moderate doses intravenously have been voiced (189).

DiGeorge *et al.* (190) have shown that long-standing hypothyroidism may lead to decreased TSH production by the pituitary gland. The radioiodine space is increased in hypothyroidism (191). Hypotonia of gallbladder (192) and urinary bladder (193) have been demonstrated in myxedema. The presence of hirsutism in infantile hypothyroidism has been reaffirmed (194). The frequent development of hypothyroidism following surgery for Hashimoto's struma has been pointed out (195, 196). The sex incidence of hypothyroidism is preponderantly female (197).

Thyroid cancer.—Several statistical analyses on thyroid cancer have been performed (198 to 201). The greater predilection of the lesion for the female is restated, as is the increased incidence of nonpapillary lesions in older patients. There has been some disagreement as to the proper surgical procedure to be carried out in the presence of metastases or for the different cell types of carcinoma encountered. Some clinicians (199, 202) are not

guided by histological typing, whereas others (203) make allowances for it, believing that papillary cancer may be treated less radically.

Radioiodine in the diagnosis and treatment of thyroid cancer is more useful after ablation of the normal thyroid tissue. Difficulties and complications arising from the use of radioiodine in this disorder have been described (204, 205, 206). The limiting factor of bone marrow damage seems to be avoided by the use of single doses of less than 150 mc. at intervals of two or more months (206). Sonenberg & Rall (204) have reported the development of pulmonary fibrosis following I^{131} therapy when pulmonary metastases are present. Seidlin and his co-workers (207) have reported two cases of acute myeloid leukemia following radioiodine therapy carried out over a period of five or six years. The doses were, of course, much larger than those used in the therapy of hyperthyroidism. Thomas (208) reports the occasional beneficial results of the use of desiccated thyroid in thyroid cancer.

The role of x-ray treatment to the head, neck, or chest in the subsequent development of childhood thyroid cancer has received further attention. Majarakis *et al.* (209) add a new series of children with thyroid cancer to those already reported in which there was a high incidence of previous irradiation, but Uhlmann (210) points out the lack of positive proof that a causal relationship exists. Until the subject is clarified, x-ray therapy to the neck region in children should be used only when absolutely indicated. Childhood thyroid cancer seems to be increasingly prevalent (211).

Thyroiditis.—Several authors have reviewed the pathological alterations, diagnosis, and treatment of the various inflammatory lesions of the thyroid (212, 213). Interest has been aroused in the finding of abnormal serum protein electrophoretic patterns in Hashimoto's struma, often with normal total serum protein measurements and elevated colloidal gold and cephalin flocculation tests (214, 215). Roitt *et al.* (216) have shown that patients with struma lymphomatosa have precipitins in their sera which react specifically with thyroglobulin. They propose that these patients are autoimmunized against thyroglobulin and that the thyroidal lymphoid infiltration represents the interaction of the thyroglobulin in the gland with the autoantibodies of the serum. Owen & McConahey (217) have detected the presence of an abnormal iodinated protein in the serum of patients with Hashimoto's struma which may be thyroglobulin. Morgans & Trotter (218) have presented evidence of defective organic binding of iodine by the thyroid involved by Hashimoto's disease. Luxton (219) has found a high incidence of Paget's disease in patients with struma lymphomatosa. Wollner *et al.* (220) have established criteria for the diagnosis of Riedel's struma and stressed the pathological differences between it and struma lymphomatosa.

Stemmermann (221) has reported two patients with subacute thyroiditis with elevated alpha-2 globulins in their serum. Skillern *et al.* (222), reviewing the findings in 66 patients with subacute thyroiditis, have called

attention to the frequent occurrence of anemia in this disorder and to the fact that the colloidal gold test is usually normal. The beneficial effect of cortisone in the treatment of subacute thyroiditis has been reaffirmed (222, 223).

Thyroxine and its analogues.—A prolific field of thyroid research has been that of the metabolism of thyroxine, its analogues, and its precursors. It is now generally accepted that mono- and diiodotyrosine do not normally appear in the general circulation, but are enzymatically dehalogenated in the thyroid and probably elsewhere, the freed iodide recirculating for further use by the thyroid (172, 224, 225). Mono- and diiodotyrosine have been shown to have no metabolic effect when administered to a patient with myxedema (226). On the other hand, extensive study of *l*-triiodothyronine has shown it to be the most potent of all thyroid metabolites (227), being about three to four times as potent as *l*-thyroxine. The analogue 3-3′-diiodo-5-bromthyronine possesses slightly less antigoitrogenic activity than triiodothyronine (226). In general, the three-halogenated thyronines are more potent than the corresponding four-halogen thyronines, although Mussett & Pitt-Rivers (228) have pointed out an exception. These authors have also defined the halogenation of thyronine which must exist for the molecule to have physiologic activity.

It is likely that *l*-thyroxine is converted to *l*-triiodothyronine in the peripheral tissues, and that the thyroid is not the principal site of formation of triiodothyronine (227, 229). There is some evidence, however, that the conversion of thyroxine to triiodothyronine is not the main pathway in the metabolism of thyroxine (230). Thyroxine travels in the blood between the alpha-1 and alpha-2 globulins and is firmly bound by a thyroxine-binding protein (TBP). Studies on the uptake of *l*-thyroxine and *l*-triiodothyronine by red cells have shown that thyroxine is more firmly bound to plasma proteins and takes longer to disappear from the plasma than triiodothyronine (231, 232). The degradation of thyroxine is slowed in myxedema and increased in hyperthyroidism (229), and Vanarsdel & Williams (233) believe that in myxedema there is impairment of hormone transfer across the cell membrane. It has been shown that the posterior pituitary concentrates both thyroxine and triiodothyronine in greater amounts than other areas of the brain (234), and it is suggested that the neurohypophysis possibly regulates the production of TSH by the anterior pituitary.

Triiodothyronine increases the rate of protein synthesis in hypothyroid subjects; the reverse occurs in normal subjects, showing that an excess of hormone apparently decreases protein synthesis (235) Triiodothyronine improves renal function in myxedema and produces negative nitrogen balance long after the patient has returned to euthyroidism clinically (236, 237). The cellular mechanism of action of triiodothyronine has not been established. There is evidence that it has an effect on the transfer of energy-rich phosphate bonds (238, 239).

In 1955, Thibault & Pitt-Rivers (240) reported that the acetic acid

analogues of triiodothyronine and thyroxine differ from their parent compounds in producing an immediate rise in oxygen consumption in rat kidney slices. For this reason, they conjectured that the acetic acid analogues may be the form in which the hormones act in the tissues. Albright *et al.* (241) have reported the existence of an enyzme system for the conversion of thyroxine and triiodothyronine to their respective acetic acid analogues in rat mitochondria. Triiodothyroacetic acid has been recovered from rat kidney following injection of triiodothyronine (242). The acetic acid analogues have weaker activity than their respective parent compounds (243, 244). The metabolic effect of tri- and tetra-iodothyroacetic acid in euthyroid and myxedematous patients has been recently studied (244 to 248). A dissociation of action of triiodothyroacetic acid in small doses has been noted with little effect on BMR but with pronounced decrease in serum cholesterol concentration (243, 245). Other investigators, however, have not noted this dissociation (247). Rall *et al.* (244) find little difference in action between triiodothyronine and triiodothyroacetic acid. Triiodothyroacetic acid has no effect on the cholesterol content of the aorta of rabbits (248). The formic acid analogue of thyroxine, however, has been found to have a relatively greater effect on cholesterol metabolism than on goiter prevention in animals (246). The final answer to the place of the acetic acid derivatives in the metabolism of thyroid hormone remains to be clarified.

Miscellaneous.—Most of the de-iodination of thyroxine and triiodothyronine has been reported to occur in the liver (249). Mechanisms of action of the antithyroid drugs have been studied (250, 251). Propylthiouracil has been shown to slow the degradation of triiodothyronine and thyroxine *in vivo,* but the locus of its action was not found. Other facets of the peripheral effects of thyroxine have been investigated. The administration of thyroxine with cortisone and deoxycorticosterone has been shown to aggravate the cardiac and renal lesions produced by the latter two drugs and to cause a clinical picture not unlike eclampsia (252, 253). The synergistic action of thyroxine and epinephrine has again been demonstrated (254). Triiodothyronine induces an increase in production of androsterone relative to etiocholanolone in the degradation of testosterone (255).

Friis & Hall (256) have reported failure of thyroxine to cross the placental barrier, although Grumbach & Werner (257) have found it to cross slowly, while triiodothyronine crosses more readily. Postel (258) has shown that in the guinea pig perchlorate crosses the placental membrane, but triiodothyronine does not. The thyroxine-binding capacity of the plasma has been shown to be increased in pregnancy (259), but whether this is due to an increase in the amount of thyroxine-binding protein or to an increase in the affinity of protein for thyroxine is not known. The same changes in PBI and thyroxine-binding capacity of the serum were produced by administering stilbesterol to nonpregnant women (259). Feldman & Danowski (260) have gathered evidence that estrogen increases the quantity of PBI turned over daily in rats, and Feldman (261, 262) has presented further

evidence that estrogen has a direct action on the thyroid gland. Estrogen impairs goiter formation in adult rats given propylthiouracil (263). Young women show no change in the level of PBI following bilateral oophorectomy (264).

The effects of thyroxine on the pituitary (265), on serum albumin (266), and on the circulation (267) have been reported, as well as its action on wool growth in sheep (268). Rats rendered hyperthyroid by thyroid administration have been shown to avoid alcohol; this finding may be significant in the treatment of alcoholism (269).

The content of radioiodine of human and animal thyroid glands obtained in various sections of the country following the nuclear bomb tests has increased, but the rise is below the range viewed as harmful (270, 271). Marks *et al.* (272) have reported the pathological effects on the thyroid gland of long-term ingestion of I^{131}.

Adrenal Cortex

Assay and tests of function.—Methods of measurement of the corticoids have been improved, and this subject has been reviewed by Gold (273). A modification of the method devised by Nelson & Samuels for the determination of hydrocortisone in plasma and urine has been developed by Silber & Porter (274). Further modifications leading to a highly sensitive chemical assay for plasma hydrocortisone have been described by Silber & Busch (275), Peterson *et al.* (276), and Eik-Nes (277). These procedures employ the Porter-Silber color reagent, phenylhydrazine-sulfuric acid-ethyl alcohol. This reagent has also been used in the assay of tetrahydrohydrocortisone and tetrahydrocortisone (278). The Porter-Silber reaction appears to be a more accurate method for assaying adrenocortical hormones than that which utilizes blue-tetrazolium as the color reagent (279). Technical factors in the use of blue-tetrazolium have been discussed (280). Chromogens in urine prevent accurate chemical assay of steroids; Antunes (281) has successfully removed such chromogens by the addition of formaldehyde to the urine prior to steroid extraction. The importance of various technical factors in the chemical assay of plasma hydrocortisone has been shown by Harwood & Mason (282). An extraction tube of glass has been described (283). The importance of the selection of the solvent used in the extraction of steroids has been pointed out (284). A procedure for the determination of 11-oxygenated, 17-ketogenic steroids in urine has been outlined by Wotiz *et al.* (285); in this assay the steroids are isolated by paper chromatography and measured colorimetrically by the Zimmermann reaction. The technical advantage of using *N*-benzyltrimethyl ammonium methoxide rather than potassium hydroxide in the Zimmermann reaction has been described (286). A colorimetric method for the chemical determination of aldosterone has been recorded (287, 288).

Eosinopenia in the guinea pig does not always occur upon the administration of ACTH, yet Schweizer (289) notes that if the number of eosinophils

is related to the number of polymorphonuclear cells, there is a consistent decrease in the relative numbers of eosinophils after administration of ACTH. The eosinophil count has also been used to show that adrenalectomized rats exposed to cold fail to show a reduction of eosinophils upon the administration of a dose of cortisone known to be effective when the animals are at room temperature (290).

Hyperadrenocorticism.—The chemical and clinical aspects of adrenal cortical disorders have been excellently reviewed by Prunty (291), the treatment of adrenal disease by Thorn *et al.* (292) and the diagnosis and treatment of adrenal adenoma and hyperplasia by Dahl-Iversen (293). There has been discussion whether or not Cushing's disease is primarily an adrenal or a pituitary disorder. Although much evidence suggests that adrenal hyperfunction per se is responsible for the disease, such does not account for remissions which may follow partial or complete destruction of the pituitary. This has led Jailer *et al.* (294) to postulate that the pituitary also secretes a substance which potentiates the action of ACTH and that Cushing's disease results from excess production of this factor. Means of delineating patients with Cushing's disease who have hyperplasia from those with tumor of the adrenal cortex have been shown by Soffer *et al.* (295) and by Sandberg *et al.* (296); upon the administration of ACTH the plasma level of 17-hydroxycorticoids fails to increase in patients with tumor but usually increases markedly in those with hyperplasia. Differentiation is also possible by chromatographic analysis of the 17-ketosteroid, dehydroisoandrosterone (297); in patients with adrenal tumor urinary excretion of this steroid is diminished, whereas in those with hyperplasia it is increased.

Henneman & Bunker (298) have shown that levels of inorganic phosphorus are decreased and levels of lactate and pyruvate are increased in venous blood of patients with Cushing's disease and in subjects receiving corticosteroid therapy; they postulate that the adrenal steroids inhibit the oxidation of pyruvate to carbon dioxide and acetyl-CoA.

X-ray treatment to the pituitary region brings improvement in about half of the patients with Cushing's disease due to adrenal tumor; it appears that improvement is more likely to occur if the radiation is intense over a short period of time (299).

A patient with clinical manifestations of Cushing's disease was observed to have a spontaneous recovery followed a year later by recurrence of the disease; Zondek (300) believes that a hypothalamic origin must be considered. Cushing's disease, in association with carcinoma of the bronchus, has been reported in a woman of 55 years (301); this is the fourth case report of this unusual association. The fifth instance of Cushing's disease in association with carcinoma of the pancreas has been described (302). Ovarian carcinoma with Cushing's disease has also been reported (303). The relationship of Cushing's disease to various cancers has been discussed by Thorne (304).

The appearance of the renal glomeruli, studied in two patients with Cush-

ing's disease, resembles somewhat the changes found in toxemia of pregnancy (305); there is a broadening of the capillary walls of the glomeruli. The cardiovascular and renal complications of Cushing's syndrome have been reviewed (306). In 17 patients the clinical and autopsy data show a high incidence of hypertension, congestive heart failure and cardiomegaly, as well as nephrocalcinosis. The controversial role of the adrenal cortex in the production of essential hypertension has been discussed in the *Lancet* (307).

The effectiveness of various steroid preparations in the treatment of adrenal virilism has been studied by Spence *et al.* (308). The response to cortisone given orally is unreliable, but to prednisone or prednisolone the improvement is excellent and the disorder well-controlled. Good control was also obtained by administration of hydrocortisone intramuscularly weekly or biweekly. Skoog & Adams (309) found also that prednisone, 10 mg. daily, is effective in inducing clinical improvement and in suppressing the formation and excretion of 17-ketosteroids. That severe psychoses may be associated with adrenal virilism has been pointed out by Allen (295, 310) and by Bennet (311). Keller (312) has isolated cholestane-dione-3, 6 from a large adrenal tumor which had been removed from a virilized young woman. This steroid, never previously found in such tumors, probably represents an intermediate between cholesterol and the androgens.

Hypoadrenocorticism.—The centenary of Addison's disease has been observed (313). Treatment of Addison's disease with extracts of adrenal gland, first tried by Osler more than 50 years ago, began in concerted effort in 1930 (314). The occasional familial occurrence of Addison's disease is now recognized (315), as well as its association with thyrotoxicosis (316), and with hypoparathyroidism and moniliasis (317). Hills *et al.* (318) have compared patients with spontaneous Addison's disease with those whose disorder was induced by adrenalectomy. Pigmentation was less in the latter group, undoubtedly a result of immediate replacement therapy with cortisone at the time of adrenalectomy. Otherwise the groups were similar. In patients with Addison's disease there is diminished gastric production of uropepsin, whereas the converse occurs in patients with Cushing's syndrome (319). Yet, in normal subjects no change in pepsin secretion occurs during infusions of cortisone, hydrocortisone, or prednisolone, although aldosterone increases pepsin output (320).

A condition called "partial" Addison's disease is described; such patients have a few, mild symptoms but have normal electrolyte and hormone values at rest; on administration of ACTH, however, their adrenals respond inadequately (292, 296, 321). In pellagra severe Addisonian crisis may occur, this surely being due to atrophy of the zona glomerulosa of the adrenal cortex (322). And now, physicians must be alert to iatrogenically-induced adrenal insufficiency following withdrawal of prolonged, intense steroid therapy. Crisis has been reported in a patient with pneumonia who had received cortisone for arthritis (323). For patients who have previously

been given a therapeutic course of cortisone or one of its analogues, a test of their ability to conserve salt during a period of low salt intake has been devised as an index of adrenal function; this test has been employed by Nicholas *et al.* (324) before submitting such patients to elective orthopedic surgical procedures.

Since effective replacement therapy is available for Addison's disease, an increasing number of successful pregnancies in such patients has been reported (325, 326). The anencephalic infant usually has hypoplasia of the adrenal, the fetal cortex often being absent. The level of 17-ketosteroids in the plasma of such an infant at 12 hr. after birth was found to exceed that of healthy adults, although later at autopsy the adrenals were approximately one-tenth normal size (327). It seems likely that the placenta was the source of the steroids.

Further observations on the use of 9-alpha-fluorocortisone in Addison's disease have been made by Leith & Beck (328). This steroid has potent salt-retaining properties (329) with comparatively little glucocorticoid effect. Dosage of 0.05 mg. together with hydrocortisone, 5 mg., each given twice daily, is recommended. Owen *et al.* (330) find that 9-alpha-fluorohydrocortisone readily produces edema without hypertension, later hypertension without edema, in Addisonian patients. On the other hand, Hart prefers this compound to deoxycorticosterone (331). It is clear, however, that this steroid must be used cautiously with close attention to dosage.

Steroid metabolism.—Following intravenous administration of hydrocortisone to a normal subject and also to an Addisonian patient, the plasma level of hydrocortisone returns to its preinfusion value in about 8 hr.; the period of diminished potassium excretion lasts about 8 hr., whereas that of sodium retention and nitrogen loss is prolonged (332). Ether anesthesia induces a marked rise in plasma hydrocortisone levels, but no rise occurs during induction with thiopentane and nitrous oxide (333). Exposure to increased concentrations of CO_2 also induces a rise in plasma hydroxycortisone (334), as does anxiety in monkeys produced by altering conditioned reflexes (335). In patients with anxiety the rate of hydrocortisone production is accelerated above normal (336). Ulrich & Long (337) have examined the theory that stress causes increased utilization of hydrocortisone and cortisone, and under the conditions of their experiment in rats they were not able to support the theory.

In rats given labelled hydrocortisone there is rapid incorporation of approximately one-half of the radioactive steroid in skeletal muscle, but within 1 hr. only two per cent remains in muscle (338). The level of plasma 17-hydroxycorticoids increases during pregnancy and shows further rise during labor and delivery (339); the level decreases upon intravenous administration of large doses of testosterone (340). The biologic half-life of C^{14}-labelled hydroxycortisone and its metabolic products, as determined by measurement of the excretion of C^{14}, has been found to be approximately 5½ hr. (341). Moreover, hydrocortisone given orally enters metabolic

pathways as rapidly as when given intravenously (342). The miscible pool of hydrocortisone in normal man has been found to be between 1.1 and 2.4 mg.; the turnover rate of endogenously produced hydrocortisone varied from 17 to 29 mg. daily, and on ACTH stimulation it increased to 154 mg. daily (343). Recognizing that the adrenal normally secretes more hydrocortisone at night than during the day, DiRaimondo & Forsham (344) suggest that perhaps the bulk of replacement or therapeutic dosage of hydrocortisone should be given late at night. Following unilateral adrenalectomy the remaining adrenal begins to increase its production of hydroxycortisone in about one week (345). In man there is no enterohepatic recirculation of hydrocortisone (342, 346); the liver metabolizes hydrocortisone rapidly (347). Hydrocortisone is loosely bound to plasma proteins (348) and has greater affinity for normal human plasma than for human serum albumin (349).

The production and excretion of the hydrocortisone-like steroids appear to be under the control of ACTH, although aldosterone excretion, influenced only slightly by ACTH, is controlled by some other mechanism related to deprivation of sodium (350). It has long been known that on stimulation with ACTH the adrenal gland becomes depleted of ascorbic acid; Slusher & Roberts (351) have now shown that the adrenal loses this ascorbic acid to the blood flowing from the gland.

It has been shown that human adrenal tissue is capable of converting progesterone, 17-α-hydroxyprogesterone and 11-deoxyhydrocortisone to hydrocortisone (352). The adrenal of the rat, as well as that of the mouse (353), is known to produce corticosterone, but little if any hydrocortisone. This phenomenon, diametrically opposed to that of the guinea pig and the human adrenal, has been studied by Hofmann (354), who suggests that the rat adrenal produces hydroxylation of a corticosterone precursor at carbon atom 11 prior to hydroxylation at carbon atom 17 and that this hinders the formation of hydrocortisone. Pregnane-3-α, 17-α, 21-triol-20-one (tetrahydro S) has been found in largest quantity in the urine of patients with adrenal tumor (355). Moreover, pregnane-3-α, 21-diol-11, 20-dione (tetrahydro A) has been found in the plasma of children receiving ACTH (356). Tetrahydrohydrocortisone and tetrahydrocortisone have been isolated from ox bile and human urine (278, 357). Corticosterone has been found in the plasma of normal subjects, the level being 1.1 μg. per cent; the ratio of hydrocortisone to corticosterone was 15 to 1 (358).

Tomkins (359) has been studying the specificity of certain enzyme systems in the interconversions of various steroids. Reduced pyridine nucleotides act as hydrogen donors in the enzymatic reduction of several α, β-unsaturated 3-ketosteroids to the saturated 3-ketosteroids; moreover, the enzyme which reduces cortisone was specific, affecting no other closely related analogues (360). It is probable that there is more than one enzyme inducing hydroxylation at the 11-β position with a likely specificity for each steroid affected (361).

Bongiovanni & Eberlein (362) have sought an explanation for the fact that whereas blood contains greater quantities of dehydroepiandrosterone than androsterone, the opposite exists in urine; the answer was found in the fact that renal tubular excretion of androsterone is rapid, but the kidneys excrete dehydroepiandrosterone poorly.

In some patients with hepatitis the excretion of 17-ketosteroids is diminished, presumably because of failure of the liver to convert corticosteroids (363). In dying patients, on the other hand, the plasma 17-hydroxycorticoids attain high levels, presumably due to failure of the body to metabolize the steroids during the agonal state (364). In patients with chronic asthenia the urinary excretion of 17-ketosteroids is diminished, while that of cortisone-like compounds is increased; the response to ACTH stimulation is diminished (365).

Miscellaneous.—The U. S. Department of Agriculture has stated that the plant, *Agave lecheguilla,* a weed toxic to some animals and growing in abundance in Texas, is a rich source of steroids which can be used as precursors in the synthesis of cortisone (366).

Prunty and his associates (367)have identified a new steroid, wildegosterone, possessing salt-retaining properties; this compound is found in the urine of some patients with edema and of women in late pregnancy. The salt-retaining properties of 1-dehydro- and 1-dehydrohydrocortisone, new synthetic analogues of cortisone and dehydrocortisone, respectively, have been found to be relatively minute (368). These analogues are excreted in the urine, for the most part unchanged and unconjugated (369). Analogues of deoxycorticosterone, compounds dehydrogenated at carbon atoms 1 or 2, showed salt-retaining properties similar to their parent substance. The compound, 1-dehydro-9-alpha-fluorohydrocortisone, is as potent as aldosterone, and readily produces hypertension in adrenalectomized rats (370). de Gennes *et al.* (371) state that 2 to 6 mg. daily of 9-alpha-fluoro-1-dehydrodehydro-cortisone given for six days to a patient with Cushing's syndrome induced marked reduction in urinary excretion of 17-ketosteroids and hydroxycorticoids. Ventura (372) has shown that nephrosclerosis, edema, and myocarditis induced in rats with 1-dehydro-9-alpha-chlorodehydrocortisone is lessened by either thyroidectomy or adrenalectomy. Two other analogues of hydrocortisone have received careful study. The first of these is 2-methyl-9-alpha-fluorohydrocortisone which is far more potent than aldosterone or deoxycorticosterone in promoting salt retention (373, 374, 375) and in anticortisone effect (376) and, indeed, it induces hypertension, periarteritis, and nephrosclerosis (377). The other is 2-methyl-9-alpha-chlorohydrocortisone, which has similar but less intense properties (376, 378). These methylated compounds owe their potency to the likely possibility that they are only slowly metabolized in the body. Finally, the analogue 1-dehydro-6-methyl-hydrocortisone, is a glucocorticoid which promotes excretion rather than retention of salt and water (379).

The remarkable inhibitory effects of amphenone on the adrenal cortex

have been reviewed (380, 381). This drug, among its other properties, prevents synthesis of aldosterone and is therefore effective in hyperaldosteronism (382). Steroid production by tumor of the cortex is also blocked, although no lytic effect on the tumor has been noted (383). Side effects of amphenone are distressing, but the recognition that amphenone is a chemical inhibitor will surely stimulate a search for other similarly potent, less toxic compounds.

An adrenocorticolytic drug has been found in the complex organic compound 2, 2-*bis* (*para*-chlorophenyl) -1, 1-dichloroethane (384, 385). In dogs a selective necrosis of the adrenal cortex can be achieved which may prove fatal unless cortisone is administered (386). It has been stated recently that the true adrenolytic agent is a contaminant in the compound (386).

The British experience with the steroid anesthetic, 21-hydroxy-pregnane-3: 20-dione sodium succinate (Viadril), is of interest (387). Dosages of 500 to 1000 mg. are given intravenously and induce quiet sleep usually within 5 min. (388). A sense of well-being characterizes the recovery period. The anesthetic properties of Viadril relative to other well-known anesthetics have been set forth by Galley (389).

The Parathyroids

Bone.—Several excellent reviews on the subjects of bone physiology (390 to 393) and of the skeleton in disease states (394, 395) have appeared and bring up to date the general state of knowledge on this subject. It now appears certain that crystalline collagen, the organic phase of bone, is derived from bone cell secretion. The collagen initiates inorganic hydroxyapatite bone crystal formation, and there is a close physical, and probable chemical, association between the organic and inorganic phases. A dynamic state of ion transfer exists between bone crystals (their interior, their surface, and a three-layered hydration shell bound to each crystal) and the extracellular fluid; it is through this complex system that calcium and phosphorus are delivered from serum to bone and back again (391). Studies have shown that intravenously administered Ca^{45} disappears rapidly from the blood into the interstitial space and into bone and that the transfer into bone is so rapid that the intravascular and interstitial spaces may be considered as a single compartment (396). It has also been demonstrated that the rate of calcium mobilization from bone is directly proportional to the lowering of the serum calcium level, suggesting that an equilibrium exists between serum calcium and the mobilizable calcium fraction in bone. Calculations have shown that in order for such an equilibrium to exist the effective bone blood flow must range from 3 to 7 per cent of the resting cardiac output (396) and that this equilibrium alone would maintain the serum calcium at a level of 5 to 7 mg. per cent (392).

Calcium, phosphorus, and parathyroid hormone.—There are other factors, however, than the physico-chemical equilibrium state between bone and plasma which are involved in and influence the metabolism and main-

tenance of body calcium and phosphorus. It has now been generally accepted (396) that the principal action of PTH is on the mobilization of calcium from bone. The mechanism of this action is not clear, but Talmage & Elliott (397) have shown that in rats the extrarenal influences of parathyroid hormone (PTH) may be noted as quickly as the renal effects. After nephrectomy the changes produced by PTH administration in the extracellular concentration of calcium, phosphate, and citrate ions are of approximately equal magnitude and in the same direction. Thus, PTH seems to cause mobilization of both calcium and phosphate from bone. This finding has been supported by data obtained by Manunta *et al.* (398) from the use of Ca^{45} in rats; PTH was shown to cause rapid decrease in serum and bone radioactivity, indicating an acceleration of turnover of calcium.

Citric acid may be of importance in the mechanism of PTH action on bone. Neuman *et al.* (399) have shown that PTH produces a prompt increase in the arteriovenous difference in citrate levels in venous outflow from bone. In nephrectomized animals the administration of PTH produces an increase in the level of serum citrate, as well as that of calcium and phosphorus (397, 400). These findings indicate that local pH changes or chelation effects of citric acid may be important factors in PTH effect on calcium and phosphorus mobilization. Elliott & Freeman (401) have further shown that PTH produces a relatively greater rise in the level of serum calcium than in that of citric acid, and that a single dose of PTH produces a rise in serum calcium without necessarily any change in citrate level. On the other hand, Canary & Kyle (402) have shown that in man the infusion of saline alone produces a rise in the level of serum citrate comparable to that obtained by calcium infusion, and Freeman & Elliott (403) have found that a considerable turnover of citrate occurs in the absence of the parathyroid glands. Such observations suggest that changes in levels of serum citric acid previously noted in many skeletal disorders may arise from the basic disease process and may not depend on changes in serum calcium or phosphorus.

The finding of Engel (404) that parathyroid extracts produce an elevation of the blood level of seromucoid in rats suggests the possibility of a specific action of PTH on bone matrix. Shetlar *et al.* (405) find increases not only in seromucoid after PTH but also in serum glycoprotein. Administration of formaldehyde-treated PTH induces no rise in the level of serum calcium, although the response of the seromucoid level to this preparation persists. These results indicate that PTH affects seromucoid independently of its action on calcium. It is indeed now considered that two parathyroid hormones may exist (391).

PTH tends to increase the ionized fraction of calcium in serum. Manunta *et al.* (406) have employed radioactive calcium and electrophoretic techniques to study the binding of calcium to protein; they find that following parathyroidectomy a decrease in albumin-bound Ca^{45} and an increase in the alpha-globulin-bound Ca^{45} occur. The addition of inorganic phosphate

to PTH prior to administration of this mixture to parathyroidectomized rats causes suppression of the calcium-mobilizing activity of the PTH. This effect is probably caused by direct interaction of the phosphate with PTH (407).

The action of PTH on renal function has been further investigated. Hiatt & Thompson (408) have shown that the intravenous administration of PTH in normal man produces phosphate diuresis by a rise in filtered phosphate secondary to a rise in glomerular filtration rate (GFR) without a decrease in tubular threshold for phosphate (Tm_P). In hypoparathyroid individuals given PTH, however, there is an accompanying decrease in Tm_P, as well as an increase in GFR. Acute administration of PTH produces these changes in renal hemodynamics without inducing hypercalcemia, whereas prolonged subcutaneous administration of PTH produces both hypercalcemia and decrease in Tm_P. In man, calcium infusion produces a fall in urinary phosphate which results from an increase in tubular reabsorption of phosphate. Administration of PTH in constant amounts abolishes this tubular response to calcium infusion.

The place of vitamin D in the metabolism of calcium and phosphorus has been further clarified. In addition to favoring the absorption of calcium and phosphorus from the intestine, vitamin D in rachitic children causes a direct increase in the bone salt accretion rate. It also produces an increased bone salt resorption rate, an action not unlike that of PTH (409). Moreover, Crawford *et al.* (410) have found that vitamin D in large doses has a demineralizing effect similar to that of PTH and no direct parathyroid suppressive action. They have shown further that rats fed a low calcium diet and given large doses of vitamin D develop a convulsive disorder suggestive of tetany. Since levels of serum calcium remain near normal in these rats and there is no parathyroid hypertrophy, the authors suggest that an increased accumulation of citrate found in muscle, bone, and kidney of these animals causes peripheral nerve toxicity. Elliott & Freeman (400, 401) have presented evidence that Vitamin D and PTH have independent and dissimilar actions on citric acid metabolism.

The effect of estrogen on calcium and phosphorus has also been further studied. Manunta *et al.* (398) have found that estrogen decreases the urinary excretion of calcium and augments absorption of calcium from the gut. They also have established that estrogen produces changes in the protein-binding calcium in the serum (406). The relative effects of various estrogens on bone can be accurately determined by measurement of the changes in bone density in mice produced by estrogen administration (411).

Krane *et al.* (412) have measured body calcium compartments, the calcium pool, and the rate of bone blood flow in four hyperthyroid patients; their data indicate increased rates of osteogenesis and osteolysis in thyrotoxicosis.

At the renal level, Thompson & Hiatt (413) have shown that daily administration of phosphate seems to produce a direct effect on the renal

tubule of decreasing phosphate reabsorption, and reduction of serum calcium was not a factor in this effect. These investigators have further shown (414) that Tm_P is variable from individual to individual and even in the same individual at different times; this variabilty is unexplained, but points out the impossibility of standardization of this measurement, as compared, for instance, to Tm_G. This difficulty has been discussed also by Fraser (415).

Bronner *et al.* (416) have studied the relative importance of fecal and urinary excretion of intravenously administered Ca^{45} and have shown that, although there is great species variation, in man, at least, the urine is the more important route for excretion of endogenous calcium. The subject of calcium and phosphorus metabolism has been extensively reviewed (417).

Hypercalcemic states.—Bogdonoff *et al.* (418) have recently reviewed the experience with hyperparathyroidism at Duke University Hospital, emphasizing certain clinical aspects of diagnosis and management, such as the occurrence of multiple-system involvement, the occasional presence of extensive vascular calcification, and the importance of electrocardiographic changes. Myers (419) has reviewed the symptoms and treatment of hypercalcemia. Goldzieher *et al.* (420) have presented three cases illustrating the difficulties sometimes encountered in making a correct diagnosis of hyperparathyroidism. In each patient the calcium infusion test was misleading, the measurement of tubular phosphate reabsorption was informative in two, and the phosphate deprivation test helped to establish the diagnosis in one. Chambers and his co-workers (421) have appraised the value of these tests in the diagnosis of hyperparathyroidism; they find the results of the calcium infusion test to be inconsistent. Nine of their 10 patients with hyperparathyroidism had abnormally low tubular reabsorption of phosphate; the value of the test was improved if performed after the patient had been maintained on a low phosphate intake for three days.

Much has appeared in the British literature on hypercalcemia in infancy. The clinical picture of this syndrome is anorexia, vomiting, constipation, and failure to thrive, along with increased levels of serum calcium and blood urea nitrogen. A committee investigating this disorder noted (422) that 255 cases had been reported in England from 1953 to 1955, with the peak age incidence being between 4 and 8 months. The prevalence of this disorder in the British Isles and the rarity of its recognition in North America led to an investigation by the committee to determine the vitamin D content in British foods. It was found easily possible for infants in Britain to receive relatively large amounts of supplemental vitamin D in their daily diet. The committee (422) recommended reappraisal of the practice of adding vitamin D to food, and added that they had not found a case of hypercalcemia in an infant who had been entirely breast-fed. Although various etiologic explanations have been offered, the prevailing theory is that the condition results either from vitamin D intoxication or from vitamin D hypersensitivity. Forfar *et al.* (423), on the other hand, have shown that two hypercalcemic infants were not sensitive to large doses of vitamin

D; since five of his six cases had an increase in serum cholesterol, he postulates that faulty fat metabolism may be an etiological factor.

The finding of hypercalcemia in some patients with sarcoidosis has received attention. Mather (424) has found an elevated serum calcium level in 4 of 86 patients with sarcoid; the increase is in the ionizable form of calcium, and it is not likely to come from parathyroid, renal, or serum protein abnormalities. One of these four patients had an excessive absorption of calcium from the gut when given vitamin D. Scholz & Keating (425) have studied eight cases of sarcoid with renal involvement; six had hypercalcemia and two were hypersensitive to vitamin D. Henneman *et al.* (426) has investigated three subjects with sarcoid and hypercalcemia, observing that all had balance studies suggesting endogenous vitamin D intoxication. They find that sodium phytate is effective in decreasing hypercalciuria and intestinal absorption of calcium, and recommend its use in the treatment of the hypercalcemia of sarcoid. McSwiney & Mills (427) have reviewed this subject, and have pointed out that hypercalcemia is apparently the major cause of renal disease in sarcoidosis.

Several articles have appeared on vitamin D intoxication. Scharfman & Propp (428) have emphasized the occurrence in this condition of normocytic anemia which seems to result from renal impairment. Freedman (429) has reported an individual who developed renal colic from vitamin D overdosage; after discontinuance of the vitamin D medication, hypercalciuria was still present 15 months later. Eisenstein & Groff (430) have produced experimental vitamin D intoxication in rats, and report the development of metastatic calcifications in blood vessels and heart, increase in levels of serum seromucoid and myocarditis. Experience with eight cases of the milk-alkali syndrome has been reviewed by Scholz & Keating (431), who emphasize that a feature of importance in diagnosis is the lack of hypercalciuria in the presence of hypercalcemia, and a striking characteristic in most patients is the rapidity of improvement on withdrawal of the milk and alkali.

Hypercalcemia has been reported in association with Hodgkin's disease (432), acute leukemia (433), and imminent adrenal crisis (434); the mechanism of production of hypercalcemia in these conditions is unknown.

Hypocalcemic states.—Hinrichs (435) reports that the teeth are affected in juvenile hypoparathyroidism only if the disease begins during tooth formation and calcification. A delay in tooth eruption may result. Knuth & Kisner (436) have emphasized the frequency of bilateral cerebral calcifications in individuals with hypoparathyroidism and describe a patient in whom such calcifications accompanied a cystic parathyroid adenoma. Willison & Whitty (437) record a patient in whom postoperative hypoparathyroidism, when inadequately treated, brought on localized fits in association with a brain tumor.

Davies *et al.* (438) report two cases of steatorrhea in whom typical radiologic evidence of hyperparathyroidism developed. The coexistence of

steatorrhea and secondary hyperparathyroidism has been further discussed (439, 440).

Baer *et al.* (441) have studied renal function in pseudo-hypoparathyroidism. A temporary phosphate diuresis occurs in response to probenecid (Benemid) and an inconstant phosphate diuresis with acetazolamide (Diamox). A patient with steatorrhea in association with pseudo-hypoparathyroidism and amenorrhea has been studied (442). Rose (443) has reviewed types of renal osteomalacia, reporting an individual with osteomalacia secondary to isolated tubular loss of phosphate. Stanbury (444) has described the two main osseous lesions commonly occurring in chronic uremia, which are osteomalacia and osteitis fibrosa, and emphasizes that the abnormality in this condition seems to be an acquired insensitivity to vitamin D. He has also found dense bones in association with uremia (445). Hauge (446) has discussed vitamin D-resistant osteomalacia, or Milkman's syndrome, and presents a patient who has been observed for 17 years. Snapper & Nathan (447) have summarized the subject of rickets and osteomalacia.

Hypocalcemia in association with hypernatremic states (448) and in acute pancreatitis (449) has been reported. Escamilla *et al.* (450) have recorded their experience with parathyroid transplants in 11 postoperative hypoparathyroid patients; only two of these patients had "takes," and only one remains asymptomatic 19 months after transplant.

Miscellaneous.—Improved methods for the measurement of the concentration of calcium in serum and other body fluids have been developed (451, 452). A source of error in urinary assay of calcium has also been detected (453).

Several patients with osteogenesis imperfecta have been noted to have increased concentrations of acid phosphatase in their serum, yet their serum levels of calcium, phosphate, and alkaline phosphatase have been normal (454, 455). Several authors have reported on the syndrome of hypophosphatasia (456, 457).

Whedon & Shorr (458) have studied the metabolism of calcium and phosphorus during the acute and chronic phases of poliomyelitis. They have also reported on the effects of testosterone and estradiol and find that whereas testosterone reduced urinary calcium excretion, estradiol tended to cause a slight increase.

The Pancreas

Insulin.—During recent years it has become increasingly apparent that the action of insulin is not confined to a single enzyme system or reaction, but that it is involved in several different metabolic processes and has several sites of action. Ross (459) has recently shown that glucose transportation across cell membranes is as much as 50 per cent slower in alloxan-diabetic rabbits than in normal animals and that insulin accelerates this process. He considers impaired cellular permeability to glucose to be the

primary defect in diabetes mellitus, recognizing the fact, however, that other known effects of insulin cannot be explained by this action alone. Stadie (460) points out that insulin is active in the processes involved in the formation of higher fatty acids, probably by enhancing the condensation and hydrogenation of acetyl coenzyme A to form butyryl coenzyme A, from which, by further condensations and reductions, the higher fatty acids are formed. He has proposed a concept of insulin action in which its function on muscle tissue is primarily to promote glucose transport across cell membranes, while in both liver and adipose tissue its action is chiefly in enzyme systems, where it enhances glucose oxidation and fatty acid synthesis, and in the liver, probably oxidative phosphorylation as well. Stimulation of oxidative phosphorylation in liver and kidney tissues of rabbits by insulin has recently been reported (461). The nutritional status of the animal has been shown to be of importance in the sensitivity of adipose tissue to insulin (462).

Mirsky *et al.* (463) have indicated the physiologic role of insulinase in the degradation of insulin in the intact animal. In fasting mice and rats a marked decrease in the rate of insulin destruction occurs, and this results from a decrease in the insulinase activity of the liver in the fasting state. Goldner and co-workers (464) have demonstrated in bull frogs, however, that the liver is a minor site of degradation of insulin, and that other loci, especially skeletal muscle and kidney, are probably more important areas of insulin breakdown. Berson and his co-workers (465) have found no alterations in the rate of degradation of insulin-I^{131} in cortisone-treated rabbits, as compared to untreated animals.

The problem of insulin resistance has received much attention. Several groups (466, 467) have shown that insulin-I^{131} remains in the plasma longer in those diabetics who had been previously treated with insulin than in either normal individuals or in diabetics who had never received insulin. This difference arises from binding of the insulin by an acquired globulin in the plasma of the insulin-treated group. That this binding probably interferes with the physiologic activity of insulin is suggested by the fact that it protects mice against insulin hypoglycemia. Further studies by Berson *et al.* (467) have shown that this globulin satisfies the requirements necessary for it to be called an antibody; they point out that since all insulin-treated patients have this antibody, its presence is not necessarily associated with loss of insulin response. Whether it is the same antibody that in very high titers is responsible for "insulin resistance" is not known. Vallance-Owen & Lukens (468) have demonstrated that there is much insulin-inhibiting activity in the plasma of depancreatized cats, but that this inhibiting factor disappears if pancreatectomy is accompanied by hypophysectomy or adrenalectomy. This insulin antagonist lies within the alpha, beta, or gamma globulin fraction of the plasma, but is not a lipoprotein similar to that described by Bornstein (469). Field & Stetten (470) have found evidence of a humoral insulin antagonist in five of seven diabetic patients in acidosis.

Moreover, Colwell & Weiger (471) have reported insulin resistance in a patient with hemochromatosis in whom the antiinsulin activity resided in the elevated gamma globulin fraction of plasma; the treatment of this patient with ACTH resulted in a decrease in insulin requirement. Hampton *et al.* (472), however, have reported two cases of insulin resistance whose insulin dosages were not lowered by cortisone therapy. Arquilla & Stavitsky (473, 474) have demonstrated that rabbit antiinsulin serum is specific for insulin obtained from five different animals, including man, and could therefore be used as an assay test for insulin resistance. In insulin-resistant subjects, the bound insulin migrates at the leading edge of the gamma globulin fraction on paper electrophoresis (475). In patients with Cushing's disease insulin resistance is not always present (476). The subject of insulin resistance has been reviewed by Voll & Kloster (476a), who have listed the various states and factors that have been implicated in its production.

The development and clinical application of new insulin preparations has been discussed by several authors (477 to 481). Most are in agreement that the insulin zinc suspensions (the lente insulins) are superior to other forms of insulin. Jersild (477) has reported a large series of diabetics in which 82 per cent of the patients were maintained in good condition on one injection of lente insulin daily.

Glucagon.—Bencosme & Frei (482) believe that glucagon is secreted by the alpha cells of the pancreas; they have shown that extracts from pancreases of guinea pigs whose alpha cells have been completely poisoned by cobalt possess no hyperglycemic effect, whereas pancreases showing lesser degrees of poisoning on histologic examination yield extracts whose hyperglycemic action is comparable to extracts of normal pancreas. This subject is controversial, however, and has been reviewed by Van Itallie (483).

There is general accord that glucagon produces an increase in phosphorylase activity in the liver, with resulting acceleration of glycogenolysis, depletion of hepatic glycogen stores, and hyperglycemia (484, 485, 486). There is apparently no true increase in glucose-6-phosphatase activity in response to glucagon (485). Although the first effect of injected glucagon is depletion of liver glycogen, several investigators have reported an increase in liver glycogen above initial levels 24 hr. after glucagon injection (484, 486). The significance of this finding is not clear. Root (484) has found that daily administration of glucagon to normal, alloxan-diabetic or adrenalectomized rats results in increased liver glycogen; on the other hand, daily administration of epinephrine results in marked depletion of hepatic glycogen stores. Costa *et al.* (486), however, have found that alloxan-diabetic rats do not respond to glucagon by an increase in liver glycogen; this led them to suggest that the increase observed in normal animals results from increased insulin output secondary to the hyperglycemia produced initially by the glucagon injection. The reason for the discrepancies in these

studies is not apparent. Both groups are agreed, however, that although epinephrine works faster than glucagon, and its effects are shorter lived, the two substances both cause hepatic glycogenolysis and phosphorylase activation. Williams and his associates (487, 488) have studied glucagon metabolism in rats and demonstrate that kidney and liver tissue concentrates glucagon-I^{131} more avidly than other tissues; in radioautographs of the kidney the concentration of the labeled glucagon is apparently greater in the proximal convoluted tubules. The liver, kidney, and muscle are likely to be especially important sites of glucagon degradation, although many tissues concentrate glucagon. Elrick *et al.* (489) have presented further evidence that glucagon may work synergistically with insulin in enhancing the peripheral utilization of glucose, although their effects on the liver and blood glucose appear to be antagonistic (490). Lazarus *et al.* (491) have shown that in rabbits pretreated with cortisone there is a marked initial rise in blood sugar following a large intravenous dose of commercial insulin. This hyperglycemic effect is due to the glucagon content in the insulin preparation and is sufficiently sensitive for use as an assay for glucagon. It is suggested that the insulin resistance seen in human beings and animals receiving both steroids and insulin may be caused in part by the glucagon content of the commercial insulin.

The aryl-sulfonylureas.—A tremendous volume of literature has appeared during the past year on the mechanism of action and clinical usage of the aryl-sulfonylureas. The subject has recently been reviewed extensively by Williams & Henley (492). The two substances, carbutamide (BZ-55) and tolbutamide (Orinase) have slightly different characteristics. Carbutamide becomes partly intracellular, while tolbutamide remains extracellular; both are bound to plasma albumin, tolbutamide more tightly than carbutamide. The largest concentrations of each in hepatic cells are in the supernatant fractions of the disintegrated cells following centrifugation (493). Tolbutamide is excreted faster than carbutamide (492), the main excretory product of the former being butyl-*p*-carboxyphenyl sulfonylurea (494).

These drugs decrease hepatic glucose output (495 to 498), and some authors have shown that they inhibit glucose-6-phosphatase (496, 499). There has also been a suggestion that the sulfonylureas inhibit phosphorylase activity (500). They have been shown not to increase muscle glycogen (501, 502), or glucose uptake by the tissues (503).

It is generally agreed that these compounds do not elicit an acute hypoglycemic response in the absence of insulin (504, 505). They may stimulate an increased production of insulin (506) by the pancreas. There is also evidence that the sulfonylureas may work by inhibiting the action of insulinase (504), although others (507, 508) find no evidence that this is their mechanism of action. There is, indeed, ample evidence that their mechanism of action is different from that of insulin (503, 509), for their administration produces no change in oral glucose tolerance tests when insulin is given, and there is no increased glucose uptake by the tissues

during their administration (502); these facts argue against an increased insulin effect. The drugs also do not appear to inhibit or affect glucagon (509), nor do they affect adrenal or pituitary secretion (494, 510). The current concepts concerning the mechanism whereby certain sulfonylureas lower the blood sugar have been concisely summarized by Levine & Sobel (511), but at present no explanation has been entirely satisfactory.

There have been reports of clinical trials with these drugs (512, 513). The impression is that the drugs are most useful in middle or older aged, obese patients with mild diabetes of the "maturity-onset" type. They are of no aid in the treatment of ketosis and are rarely of benefit in juvenile diabetics. In the dosages used, they have not appeared to increase the effectiveness of administered insulin and have not been generally shown to stabilize the insulin requirements of "brittle" diabetics. There has been a relatively high incidence (about 11 per cent) of toxic reactions from the use of carbutamide; skin rashes, bone marrow depression are among the reactions reported (514, 515, 516). Tolbutamide is a safer drug, but sufficient time has not elapsed for its toxicity to be assessed accurately.

These compounds may have a useful place in the treatment of diabetes despite the fact that we do not know how they work. "Until the mode of action has been clarified, it will be very difficult," as Stetten (517) has said, "to know with assurance whether or not we are doing the diabetic patient a favor when we lower his blood glucose concentration by the administration of a drug of the sulfonylurea group."

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ALLERGY AND IMMUNOLOGY

AUTOIMMUNITY IN DISEASE[1,2,3]

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In the past few years there has been a resurgence of interest in autoimmunity as a possible basis for a variety of diseases. This interest has been sparked in large part by observations made possible by newly developed immunologic and morphologic techniques. The demonstration of autoimmunization in both humans and animals has buried the theory of "horror autotoxicus," leaving two questions still to be answered: (*a*) in how many diseases does autoimmunization operate; and (*b*) what role does it play in those diseases? The first question may be easier to answer than the second, since there is evidence of some sort of autoimmunity in a number of human and experimental diseases. However, with the exception of the autoimmune hematologic disorders, little is known concerning the mechanisms involved in this autoimmunity or the importance of this response in the course of the disease.

By autoimmunity is meant an immune response by the host presumably manifested either by circulating antibodies or by a delayed or cellular sensitivity capable of reacting with the host's own tissues. The inciting antigen varies. In some spontaneous diseases it appears to be elements of the host tissue alone; in drug sensitivities it is a combination of the host tissue and the drug; and in experimentally induced diseases it may be provided by the host tissues or by tissues of the same or even a different species. However, regardless of the source of the inciting antigen, once the immune response occurs the corresponding tissue of the host is the principal target of the immunologic reaction and it suffers the consequences. By definition, the numerous immunologic responses which are initiated by foreign antigens and in which the host tissues may be damaged by, but do not participate in directly, the antigen-antibody reactions (such as serum sickness, anaphylaxis, the Arthus and tuberculin reactions and their related clinical entities) will not be considered in this review.

[1] The survey of the literature pertaining to this review was concluded in August, 1957.

[2] The following abbreviations are used in this chapter: AHA (acquired hemolytic anemia); LE factor (lupus erythematosus serum factor); ITP (idiopathic thrombocytopenic purpura); CNS (central nervous system); EAE (experimental allergic encephalomyelitis); EAN (experimental allergic neuritis); DLE (disseminated lupus erythematosus); DNA (deoxyribonucleic acid); RNA (ribonucleic acid).

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Several techniques have been of great importance in the advancement of this field. Freund & McDermott's development of emulsified adjuvants containing acid-fast bacilli (1) has provided a vehicle whereby autoimmunity to a number of tissues can be readily induced in experimental animals. Among those tissues to which autoimmunity can be induced with adjuvants are thyroid, central nervous system, peripheral nerves, testes, uvea, skin, articular tissues, blood cells, and lens. Establishment of a variety of sensitive methods for detection of antibodies to circulating blood cells has made possible extensive studies of human autoimmune hematologic diseases as well as of their counterparts in experimental animals [Coombs, Mourant & Race (2); Morton & Pickles (3); Diamond & Denton (4)]. The development of immunohistochemical techniques for making histologic analyses with immunologic reagents has made possible the study of human and animal tissues for antigens, antibodies, and other immunologically recognizable materials [Coons & Kaplan (5)].

The application of these techniques together with the methods of quantitative immunochemistry have gone far in implicating autoimmune mechanisms in human diseases. However, the precise nature of these autoimmune mechanisms in most instances is still not understood. This lack of understanding plus our present inability to passively transfer an etiologic agent in most diseases associated with autoimmunity makes it extremely difficult to evaluate the role of any autoimmune reaction in the pathogenesis of the diseases. For example, serum factors possessing most or all of the characteristics of autoantibodies and cutaneous sensitivity of the delayed type to autoantigens have been demonstrated in a variety of experimental and clinical diseases. However, whether these autoimmune responses mediate the essential pathologic processes in most of these diseases or whether they are merely ancillary developments in the course of the host response remains to be determined.

This review is organized according to the three types of evidence implicating autoimmune mechanisms in human diseases. First, in the autoimmune hematologic diseases of man it has been possible in some cases to demonstrate specific autoantibodies to erythrocytes, platelets, and perhaps leukocytes and to reproduce the diseases in normal volunteers by passive transfer of serum. This evidence in the human combined with comparable observations in animals constitutes the most convincing evidence of true autoimmune diseases. Second, evidence for human autoimmune disorders of the thyroid, central and peripheral nervous systems, uvea, testes, articular tissues, and skin has come in large part from the production of auto-or homoimmune responses in animals to the injection of appropriate tissues in adjuvants. The clinicopathological features of these experimental diseases resemble to greater or lesser extent certain human diseases. In addition, circulating auto-or homoantibodies and cutaneous sensitivity to the injected antigens have been demonstrated in these experimental animals, but it has not been possible to passively transfer these diseases with cells or serum.

Third, in some human diseases (disseminated lupus erythematosus, lupoid hepatitis, chronic hepatitis, and macroglobulinemia) affinity of the host's gamma globulin for constituents of his own or other tissues has been demonstrated.

Hematologic Diseases Apparently Mediated by Circulating Autoantibodies

Evidence supporting an autoimmune origin is more complete for some hematologic disorders than for any other diseases suspected of arising via this mechanism. In these disorders, partially because the involved cells are found free in the blood, sensitive immunologic techniques can be used to detect antigen-antibody reactions and quantitative measures can be applied to determine the effects of such reactions on the circulating cells. These techniques make possible the observation of effects of passive transfer of either antibody or cells, effects which might not be detectable if the cells involved were fixed in a solid tissue. Because of the relative completeness of the observations which have been made on these disorders in humans, no attempt will be made to review earlier animal work which has been duplicated and extended by most of the recent clinical observations. The animal work is of considerable interest, however, since it has aided in the understanding of the mechanisms operating in these human diseases. The autoimmune diseases involving blood cells will be discussed under the headings of the elements involved, i.e., erythrocytes, leukocytes, and platelets. However, in these diseases more than one cell type may be the target of the host's autoimmune response and such cases are being recognized with increasing frequency.

Erythrocytes.—Erythrocyte autosensitization is well-established in acquired hemolytic anemia (AHA). The use of the direct antiglobulin (Coombs) test (6) in both idiopathic (7) and symptomatic (8) types usually reveals attachment of the patient's globulin to his erythrocytes. The antibodies involved in this condition vary considerably from patient to patient in the temperatures at which they react, in the manifestations of their *in vitro* reactions and in their specificities (9 to 14). In some individual cases several different types of antibodies have been identified.

Warm antibodies, i.e., those reacting optimally at body temperature, are most frequent and are found in both idiopathic and symptomatic forms of the disease. These antibodies are usually incomplete agglutinins, rarely associated with hemolytic activity (15). These antibodies have been shown to be gamma globulins with sedimentation coefficients of approximately 7S (15a). As described by Dacie (13), patients with warm antibodies not only give a positive direct antiglobulin test of moderate titer but also frequently have a positive indirect antiglobulin test, indicating the presence of globulin in the serum capable of attaching to normal erythrocytes. Their indirect antiglobulin test is not inhibited by heating the serum, suggesting that the attachment of globulin to red cell is not dependent upon complement. The direct

test is inhibited markedly in most patients by the addition of gamma globulin to the antiglobulin test serum, which suggests that the protein adsorbed by the red cells is gamma globulin. The direct test also shows inhibition when concentrated antiglobulin serum is used, i.e., the characteristic prozone of agglutinin reactions. In addition, warm antibodies can, in most cases, agglutinate trypsinized red cells at 37°C. even at times in the absence of positive antiglobulin tests (16). In patients with warm antibodies Evans & Duane (17) have found the titres of the antiglobulin test roughly proportional to the severity of the disease.

Less frequently anti-red cell antibodies reacting optimally well below body temperature (cold antibodies) are found in acquired hemolytic anemia, either idiopathic or symptomatic, frequently with associated Raynaud's phenomena (13). Cold antibodies have been shown to be high proteins of the 19S class moving with electrophoresis as fast gamma globulins (15a, 15b, 15c). These antibodies produce red cell agglutination in high dilution at 2° to 5°C. acting usually as complete, but occasionally as incomplete, antibodies. Not infrequently they cause hemolysis, especially in acidified serum or with trypsinized cells (13, 15, 18). They are usually detected by the direct antiglobulin test in low titre and by the indirect test run at 20°C. in high titre. The direct test shows no inhibition or prozone when concentrated antiglobulin serum is used and little inhibition when gamma globulin is added to the antiglobulin serum. The latter observation suggests that proteins other than gamma globulin may be adsorbed by red cells during sensitization with cold antibodies and elicit the positive antiglobulin test. Since cold antibodies themselves have been shown to be gamma globulins (19), the additional protein adsorbed by the red cells may represent complement or other nonspecific proteins. These observations, plus the dependence of cold antibody sensitization of red cells in the indirect antiglobulin test on heat labile serum factors (20), suggest that the mechanisms of red cell coating with warm and cold antibodies are fundamentally different (13, 21).

The differences between the reaction of antiglobulin serum with red cells sensitized with warm antibody and its reaction with red cells sensitized with cold antibody, plus the studies of the nature of proteins adsorbed by sensitized red cells by Crawford & Mollison (22), Vaughan (23), and Roth & Frumin (24), bring up some of the complexities of the antiglobulin (Coombs) test. Crawford & Mollison showed the coating of the sensitized red cell could be either gamma globulin or nongamma globulin. Vaughan identified three different kinds of red cell-sensitizing proteins in patients with autoimmune hemolytic anemia. One was a gamma globulin, the second a warm-reacting nongamma globulin, and the third a cold-reacting nongamma globulin. Both nongamma globulins were found in Cohn fraction III of human serum and were thought to be either complement or complement-like substances or proteins nonspecifically adsorbed by the surface of an injured cell. Roth & Frumin found that eluates from sensitized red cells

in cases of autoimmune hemolytic anemia failed to react with red cells in the manner of an antigen-antibody reaction. Another evidence of nonimmune adsorption of serum protein to red cells is the development of weak positive direct Coombs tests in nonimmune hemolytic diseases such as sickle cell anemia. The injury of red cells by agents such as viruses can cause an adsorption of albumin by the cells with a resultant positive direct Coombs test if the test serum contains any antialbumin (25). Thus, a positive direct antiglobulin test in AHA appears to reflect, in some instances, the primary sensitization of red cell with antibody and, in other instances, the secondary fixation of serum proteins, gamma globulin or nongamma globulin, on a damaged membrane (23).

In addition to the differences in temperature requirements of antibodies in AHA, there is a marked variation in their immunologic specificities. Because autoantibodies of several different specificities as well as isoantibodies, natural or stimulated by previous transfusions, may be present in an individual patient, complete analysis of antibody specificities is difficult. Originally it was thought that the antibodies in AHA were nonspecific panagglutinins. However, since the first demonstration of antibody specificity in this disease by Weiner *et al.* (26), numerous additional observations have been published (27 to 30), and it now appears that as high as 50 per cent of patients with AHA may form single or multiple specific autoantibodies either alone or in association with apparently nonspecific antibodies (29). The specific autoantibodies are usually directed toward various Rh antigens. To demonstrate the importance of these specific autoantibodies, Hollaender (31) gave a patient with AHA associated with antibodies to his Rh antigen simultaneous transfusion of Rh positive and Rh negative blood. The Rh negative cells survived in the patient ten times longer than the Rh positive cells. Several explanations have been offered for the apparently nonspecific panagglutinins seen in patients with AHA. Crowley & Bouroncle (29) suggest that mixtures of several specific antibodies acting against several common red cell antigens could be responsible for this apparent nonspecificity. Wiener, Gordon & Gallop (32) propose that the incomplete, warm autoantibodies may be directed against the nucleus of the Rh substance, i.e., that portion of the molecule present in all individuals regardless of group specificity, and that the cold autoantibodies may be directed against the nucleus of the ABO blood group substance.

The mechanisms of autosensitization to red cells are not understood. The experimental production of autosensitization in rabbits as evidenced by the development of a positive direct antiglobulin test following injection of autologous red cells in Freund adjuvant offers one possibility [Motulsky & Crosby (33)]. This observation, together with the occasional development of hemolytic anemia in patients following hemothorax or hemoperitoneum (33), suggests that extravasated blood under certain conditions might serve as an autoantigen. On the other hand, the frequent occurrence of AHA with proliferative diseases of the lymphoid-reticuloendothelial sys-

tems suggests the possibility that abnormal growth and activity of this tissue normally responsible for antibody production might initiate the autoimmune response (8). Histochemical study of lymphomatous tissue associated with AHA offers some support for this view [Rappaport & Johnson (34)].

The immunopathologic mechanisms by which the autoimmune response leads to anemia have received considerable attention. Electron microscopic studies have revealed some of the characteristics of erythrocyte-antibody interaction. Rebuck (35) visualized the size of the reacting site of a red cell with autoantibody from a case of AHA and found it to be approximately 30 mμ in diameter. The diameter of this reacting site is approximately the same as that of the strands making up the fibrillar cytoskeleton of erythrocyte ghosts and may represent the ultimate structural unit of the red cell. In contrast, the diameter of reactive sites between anti-A isoagglutinins and A red cells was up to 24 times this size. Latta (36), also using the electron microscope to study red cell hemolysis caused by antibody and complement, found cracks developing in the red cell surface as the rigidity of the wall increased when the cell became a spherocyte.

Fixation of antibody to red cells in AHA results in a group of interrelated changes including hemolysis, hemagglutination, erythrophagocytosis, and the formation of spherocytes. The combination of these processes is responsible in this disease for the short life of the red cells, either the patient's own or transfused normal cells. In the case of normal cells transfused into patients with AHA, Selwyn & Hackett observed (37) that the normal cells became coated with the patient's globulin and were then rapidly eliminated. Since the antibodies in AHA are usually not hemolysins on the basis of their *in vitro* behavior, it seems likely that primary intravascular hemolysis is not the most important factor in erythrocyte destruction. However, antibody-induced hemolysis *in vivo* appears to be potentiated by host factors and is a much more complicated process than the prompt *in vitro* hemolysis caused by antibody and complement [Wasastjerna (38, 39)]. Antibody-induced hemolysis *in vivo* occurs in two phases: the first is prompt and involves direct hemolysis by antibody and complement; the second is delayed and probably results from mechanical trauma acting on sensitized cells in the circulating blood. Dameshek (40) has shown that red cells coated with antibody have an increased mechanical fragility and when these sensitized cells are agglutinated they are even more vulnerable to trauma. As a result of the various factors operating in the delayed phase, the hemolytic effect of antired cell antibodies *in vivo* may be as much as 100 times that observed *in vitro*, while the hemolytic actions of nonimmune agents such as saponin and streptolysin are not greater *in vivo* than *in vitro* (38).

The *in vivo* agglutination of red cells in AHA is of primary importance in red cell destruction. Factors, antibodies or other materials capable only of agglutinating red cells but not hemolysing them can produce hemolytic anemia experimentally [Castle, Ham & Shen (41)]. As with the hemolytic

activity of antired cell antibodies, their agglutinating activity is also much greater (up to ten times) *in vivo* than *in vitro*, although the nature of the enhancing host factors is not known (38). In animals with antibody-induced hemolytic anemia and in patients with AHA, direct observations of agglutination in superficial vessels have been made (38, 39, 42, 43) : agglutination of the circulating red cells was found in all AHA patients and correlated roughly with the condition of the patient (39, 43). However, Day & Perry (42) were unable to find a fall in tissue oxygen tension or in total oxygen consumption of experimental animals with severe induced intravascular hemagglutination in spite of obvious slowing of the circulation of the agglutinated cells. One of the ways in which agglutination may lead to red cell destruction is to cause sequestration of cell clumps in the spleen and elsewhere. This stasis of red cells, especially in the spleen, leads to spherocytosis and hemolysis as a result of metabolic changes presumably causing the production of hemolytic substances (41, 44).

The relative importance of erythrophagocytosis in red cell destruction in AHA is difficult to assess. That it occurs regularly in fixed macrophages and occasionally in circulating leukocytes, usually monocytes, is well-known. That erythrophagocytosis can be induced *in vitro* only by hemolytic antibodies and then only in the presence of complement has been reported by Bonnin & Schwartz (45). Their studies showed considerable parallelism between the *in vitro* conditions necessary for hemolysis and erythrophagocytosis, except that the latter occurred at greater antibody dilution. Incomplete antibodies did not lead to erythrophagocytosis nor did red cell injury produced by agents other than hemolysins (45). In apparent contrast to this observation, Zinkham & Diamond (46) found marked erythrophagocytosis in the incubated buffy coats of three of four AHA patients with incomplete antibodies. The *in vitro* phagocytosis of sensitized red cells (but not normal red cells) by splenic macrophages has also been described (47).

The spherocytosis which results from the action of antired cell antibodies is probably in itself not an important cause of red cell loss, but the spherocyte is more vulnerable than a normal red cell to each of the three foregoing modes of destruction. In addition, the spherocyte is readily removed from circulation by the spleen. The developing spherocyte undergoes changes in its intracellular protein osmotic pressure and an accompanying reduction in the tensile strength of its cell membrane [Sharpsteen (48)].

The role of the spleen in AHA is important, as evidenced by the frequent beneficial results of splenectomy in this disease. The spleen is apparently responsible to a varying degree for the formation of the antired cell antibodies (49) and is a major factor in eliminating the injured red cells, particularly spherocytes, from the circulation (50). Spherocytes are apparently too thick to pass through the slit-like spaces between the lining cells of the splenic sinuses and are therefore retained in the splenic pulp cords (51). Here they are subjected to further injury by antibody and to the phagocytic activity of splenic macrophages. The importance of the spleen

in the removal of antibody-sensitized red cells is indicated by experiments with immune hemolytic anemia which showed that splenectomized animals could tolerate larger doses of antired cell serum than intact animals (39). Detailed histopathologic study of 50 cases of AHA by Rappaport & Crosby (52) showed a high degree of correlation between spherocytosis and increased osmotic fragility of red cells and the degree of congestion of the splenic pulp cords. This congestion of the cords was in turn correlated with hyperplasia and hypertrophy of the lining cells of the sinuses. Both the lining cells of the sinuses and the macrophages of the cords contained hemosiderin, evidence of their erythrophagocytic activity. In spite of this clear evidence of splenic participation in AHA, no correlation could be found between spherocytosis or congestion of splenic cords and the patient's response to splenectomy (52).

Leukocytes.—Autoimmunization to leukocytes has been implicated in many cases of leukopenia or agranulocytosis (53 to 62). Usually these cases have also been associated with deficiencies of other blood cells and have presented as pancytopenias, either idiopathic or symptomatic, or as combined anemias and leukopenias. To date, study of these complicated cases seems to bear out the prediction of Evans & Duane (63) that the lack of each cell type is caused by the presence of separate antibodies specific for each cell type. However, the immunologic analyses of the immunoneutropenias are still unsatisfactory since the antigenic constituents of the leukocytes are not well-characterized. That human leukocytes have characteristic antigens has been demonstrated by injecting these cells into laboratory animals and obtaining appropriate antisera [for a recent report and references see Finch, Ross & Ebaugh (64)]. Tullis (65) has reported that leukocytes contain materials similar to or identical with blood group A and B substances and that they can be grouped according to the ABO system, while Rejholec and his associates (66) have identified two leukocyte antigens not correlated with red cell agglutinogens.

At present it appears that antileukocyte autoantibodies may develop (*a*) in drug sensitivity presumably to a drug-leukocyte combination; and (*b*) in idiopathic leukopenia to the leukocytes themselves. In drug sensitivity the part the leukocyte contributes to the effective antigen is not known, but the presence of the drug is apparently essential. That agranulocytosis can be precipitated by benzene, arsphenamine, and aminopyrine (Pyramidon) in sensitive patients has been clearly demonstrated [Moeschlin & Wagner (54); Dausset, Nenna & Brecy (57); Madison & Squire (67); Dameshek & Colmes (68)]. Transfer of serum from an aminopyrine-sensitive agranulocytic patient shortly after he had received the drug to healthy recipients caused a prompt fall in the number of circulating granulocytes in the recipients (54). *In vitro,* the same serum agglutinated but did not lyse the patient's own and other human leukocytes. Since these effects were noted only after ingestion of the drug, presumably the drug had to be present in the transferred serum and was an essential part of the reaction

between donor antibodies and recipient leukocytes. In a second case of agranulocytosis due to aminopyrine sensitivity it was observed that the drug was only effective *in vivo* and that *in vitro* combinations of patient's serum and drug did not agglutinate donor leukocytes (57).

Most of the autoimmune neutropenias have not been associated with a demonstrable exogenous sensitizing agent and can tentatively be considered as examples of true autoimmune responses. Agents in the sera of these patients have many but not all of the properties of antileukocyte antibodies. Discrepancies in the reported effects of these sera on leukocytes observed in different laboratories can, at least in part, be attributed to the lack of standard immunologic techniques. Observations most strongly supporting the role of an antibody in these agranulocytoses are: (*a*) Plasma transferred from an agranulocytic patient to a normal human recipient will produce a prompt agranulocytosis (57, 59, 61). Transfer of these patients' sera to rabbits causes leukopenia (59) or the formation of leukocytic emboli which lodge primarily in lungs and kidneys and are fatal (55, 56). (*b*) Sera from agranulocytic patients agglutinate normal leukocytes from almost any donor *in vitro* (57, 59, 60, 61). In one series, Dausset and his associates (57) found leukoagglutinin titers to correlate roughly with the degree of leukopenia. On the other hand, Matoth *et al.* (61) found no such correlation with several sera drawn at different times during the course of the disease in a single patient. Reports of leukoagglutinins inhibiting (57) or not influencing (61) phagocytic functions of the agglutinated leukocytes have been made. (*c*) Leukoagglutinins move with gamma globulins on electrophoresis and are stable at 56°C. and destroyed at 65°C. for 30 min. (57). (*d*) Leukoagglutinins can be removed from serum specifically by absorption on normal leukocytes and then later eluted from the leukocytes and still possess leukoagglutinin activity (57).

Several observations by Dausset, Nenna & Brecy (57) are not consistent with the operation of a usual antigen-antibody reaction in immunoneutropenias. These observations may, however, be dependent more upon the lack of appropriate techniques than upon basic characteristics of the reactions involved. These workers have been unable to demonstrate agglutination of the neutropenic patient's own cells either in his own serum, or in normal serum with the aid of antiglobulin (Coombs) serum. However, apparently some abnormalities of the patient's leukocytes are induced by his serum since these leukocytes appear to be readily phagocytosed by normal white cells (57). A similar opsonic effect of rabbit antihuman leukocyte antibodies on human leukocytes has been described (64). In regard to the preparation of leukocytes for phagocytosis, the leukoagglutinins differ from the lupus erythematosus serum factor (LE factor). The agglutinins appear to attack the neutrophils primarily, causing them to be phagocytosed by mononuclear cells, while the LE factor attacks the mononuclear cells primarily, causing them to be taken up by polymorphonuclear cells. (64).

Platelets.—Production of antibody to one's own platelets is now well-

recognized as a cause of thrombocytopenic purpura. It has been found in two situations: first, in the course of a hypersensitivity reaction to a drug in which the drug in combination with platelets makes up the essential antigen, the condition being termed symptomatic thrombocytopenic purpura; second, in the absence of any known sensitization, in which case the platelet alone is the antigen, this condition being called idiopathic thrombocytopenic purpura (ITP). In this latter group might be included those cases of autosensitization to platelets occurring in the course of diseases such as leukemia or disseminated lupus erythematosus and in other blood autoimmune disorders [Harrington (69)]. In both instances detailed study of the reaction between antiplatelet serum factors and platelets indicates that it has the characteristics of an antigen-antibody reaction. However, these immunologic studies are rendered difficult by our incomplete knowledge of the antigenic characteristics of platelets. From four (71, 72) to eight (70) antigenically distinct platelet types have been recognized so far.

In addition to the true autoantibodies, isoantibodies to other human platelets are commonly encountered and must be distinguished by suitable tests (69). Since red cell compatibility is not synonymous with platelet compatibility and since platelets are not typed in transfusion procedures, platelet isoantibodies commonly develop after several transfusions. Isoimmunization to platelets may also occur during pregnancy in a manner similar to that responsible for isoimmunization to Rh positive red cells by an Rh negative mother. Apparently, naturally occurring isoantibodies to platelets are found in from 1.5 to 6 per cent of the population (69, 71, 72). It is not uncommon to find in cases of ITP both autoantibodies to platelets which presumably caused the disease and isoantibodies which followed the transfusion of platelets or whole blood. On the other hand, some patients with ITP have no isoantibodies to platelets but do have autoantibodies against their own platelets, indicating antigenic specificity in the reaction (70, 72).

The list of drugs and chemicals believed to be capable of inducing thrombocytopenia as a result of a sensitivity reaction is long, indeed. Those drugs most carefully investigated include allylisopropylacetylurea (Sedormid) (73 to 76), quinine (77, 78, 79), and quinidine (78, 80 to 83). The immunologic mechanisms involved in the thrombocytopenias resulting from sensitivities to these three drugs are quite similar and can be considered together. Ackroyd was the first to describe this reaction in detail (74, 75, 76). He found in a thrombocytopenic patient sensitive to Sedormid that the patient's serum plus Sedormid agglutinated either the patient's or normal donor platelets *in vitro*. If complement were added to this reaction, lysis of the platelets occurred and complement was utilized in the reaction. Barkham & Tocantins (81), in testing the serum of a quinidine-sensitive patient, noted that *in vitro* lysis of platelets occurred before agglutination. As a consequence of the injury to platelets, the clot retraction of blood samples exposed to the drug and to patients' serum was reduced or elimi-

nated entirely. All three components—patients' serum, drug, and platelets—were needed simultaneously for the reaction to take place. Blood from a sensitized patient in remission, upon addition of the specific drug, became capable of platelet agglutination or lysis, or both. Bolton (83) showed, in the case of a quinidine-sensitive patient, that a complex of platelets plus quinidine absorbed antibody from the patient's decomplemented serum and that this antigen-antibody complex in turn fixed complement. When this complex was dissociated by dialysis against saline, the antibody was recovered and characterized as a gamma globulin, the antiplatelet activity of which was lost after heating to 65°C. for 30 min. The specificity of this reaction was demonstrated when it was found that quinine could not be successfully substituted for its isomer quinidine.

The *in vivo* reactions involving sensitized patient's serum, drug, and platelets resemble the *in vitro* reactions just described. Patients who have recovered from thrombocytopenia will, upon re-exposure to the drug, develop a profound thrombocytopenia within a few hours, presumably as a result of *in vivo* platelet agglutination and lysis. Steinkmap and his associates (79) transfused serum from a quinine-sensitive patient to a normal recipient who also took quinine by mouth and observed the development of a profound thrombocytopenia with purpura. Neither serum nor drug alone produced any effect in normal recipients. On the basis of these *in vitro* and *in vivo* observations, most workers have concluded that the effective antigen is a complex of platelet and drug with which the antibody of the serum reacts. However, the drug does not appear to function as a simple haptene since there is no inhibition of the reaction when the patient's serum is saturated with drug prior to exposing it to the complete antigen, in contrast to the usual haptene inhibition [Bolton (83)].

In ITP similar immunologic mechanisms appear to operate with the platelet serving as the complete antigen. Harrington (69) reports that approximately two-thirds of patients with ITP have demonstrable autoantibodies to their platelets. The immunologic character of the autoantibody-platelet reaction in ITP is somewhat more difficult to prove than in the reaction associated with drug sensitization, since, in the former, complement fixation cannot be demonstrated by conventional means (84, 85). However, Harrington (69), employing a conglutination technique, made preliminary observations which suggested complement fixation in ITP serum-platelet reactions. In most patients (21 or 31) with ITP, an antiplatelet factor or antibody which specifically agglutinated or lysed, or both, autologous and homologous platelet was identified in the serum (70). In the case of the reaction with homologous platelets both autoantibodies and isoantibodies participated. The antiplatelet antibodies were adsorbed on platelets and then eluted and still retained their activity, as shown by Stefanini and his colleagues (86). Studies of the eluted protein indicated that it was a globulin moving with beta-2 globulins in electrophoresis. Platelets taken from some patients with ITP were found to be coated with

globulin, presumably antiplatelet autoantibody (86). Normal platelets transferred to ITP patients were rapidly eliminated from the blood, while the same platelets transfused into patients with marrow aplasia persisted 4 to 6 days in the circulation (70). Transfer of ITP patients' serum or blood to normal recipients will, in most instances, cause a prompt thrombocytopenia with or without associated purpura in the recipient (70, 86). This induced thrombocytopenia may last for 1 to 2 weeks, during which time antiplatelet antibodies can be detected in the serum of the recipient and his platelets found to be coated with globulin. In some instances the antiplatelet antibody may still be demonstrable in the serum when the recipient's platelet counts are returning to normal (86).

The mechanisms by which antiplatelet autoantibodies produce thrombocytopenia and associated purpura are at least partially evident. In the development of thrombocytopenia it appears that antibody combines with platelets which may causes agglutination or lysis, as seen *in vitro,* or may merely make the platelets more susceptible to elimination by phagocytic cells of the spleen and elsewhere. That the spleen plays a significant role in eliminating platelets in the presence of antibody is indicated by the postsplenectomy improvement in platelet counts of some patients in whom antiplatelet antibodies persist in the circulation (69). Also Doan & Wright (87), using supravital stains, observed increased phagocytosis of platelets by splenic macrophages in ITP. Izak & Nelkin observed that where serum from patients with ITP was added to normal platelets and leukocytes *in vitro,* phagocytosis of the platelets resulted (88).

In addition to its effect on the circulating platelets, the antibody may injure the megakaryocytes, thereby reducing platelet formation. When serum from patients with ITP was transfused to normal recipients in amounts of 2 ml./kg., marked changes were seen in the recipients' megakaryocytes (86, 89). Within 30 min. the megakaryoctyes showed a redistribution in their cytoplasmic granules from the normal peripheral clumping to a uniform distribution throughout the entire cytoplasm. Also, platelets could no longer be identified about the megakaryocytes as in the normal. Two hours after serum transfer there was an increase in the number of immature megakaryocytes and the mature forms showed loss of cytoplasmic granules, vacuoles in cytoplasm, and degenerative changes in the nuclei. Twenty-four hours after injection of ITP serum megakaryocytes appeared normal except for a paucity of surrounding platelets. Thus, the transfer of ITP serum produced in the megakaryocytes of normal recipients most of the changes that occur in the megakaryoctes of patients with ITP [Dameshek & Miller (90)], and some of the changes seen in the megakaryocytes of animals receiving heterologous antiplatelet serum [Tocantins & Stewart (91)]. Izak & Nelkin (88), in studying *in vitro* platelet formation by normal and ITP marrow explants grown in normal and ITP serum, found that platelet formation by ITP marrow was similar in all respects to that seen with normal marrow in normal serum except that the breakdown of

the megakaryocytes into platelets was more rapid (12 to 16 hrs.) than in the normal marrow, (48 to 60 hrs). Once formed, however, the platelets in the ITP culture underwent degenerative changes and were agglutinated or phagocytosed by motile cells. In normal marrow cultured in ITP serum, platelet formation resembled but was even more rapid (4 to 5 hrs.) than that seen in the ITP marrow. Once formed, these platelets also degenerated and were agglutinated and phagocytosed. In this *in vitro* situation the effect of ITP serum on platelets was marked, but there was no evidence of injury to megakaryocytes as was seen *in vivo,* but rather only a hastening of their conversion into platelets. Perhaps factors available only *in vivo* contribute to the degenerative changes seen in megakaryocytes after transfusions of ITP serum into normal recipients.

In addition to the immunologic factors which reduce the number of circulating platelets in ITP, the operation of other mechanisms has been suggested. This suggestion is supported by the fact that in one-third of the patients with ITP no antiplatelet autoantibodies can be identified. Whether in these cases a defect in platelet production, perhaps mediated by the spleen, is responsible or whether as yet unrecognized immunologic factors are operating, or a combination of these two, remains to be determined.

The severity of the purpura in ITP is not directly correlated with the degree of thrombocytopenia. The endothelium of the small blood vessels has been implicated as a major factor in the development of purpura. What relationship, if any, the autoimmune response to platelets in ITP has with the condition of the vascular endothelium is not known. Ackroyd (76) demonstrated that a Sedormid patch test in a Sedormid-sensitive patient in remission elicited local hemorrhages in the presence of a normal number of circulating platelets. (Similar patch tests in other drug-induced thrombocytopenias have been negative, however.) From this he postulated that the capillary endothelium might behave as the platelets and with the drug form an antigenic complex which, in the presence of circulating antibody, would cause capillary damage and hemorrhage. Experiments using heterologous antisera in animals have indicated the primary role of the vascular endothelium in the development of purpura. Bedson (92) proposed that both injury to vascular endothelium which might result from any antigen-antibody reaction and a reduction in number of circulating platelets were necessary for the development of purpura. To demonstrate this he injected heterologous antirabbit erythrocyte serum into rabbits to injure the endothelium which was evidenced by endothelial swelling and distortion, and he used agar injection to reduce the number of circulating platelets, which resulted in purpura. Neither insult alone caused purpura. From this it followed that antibody to platelets might specifically reduce the number of circulating platelets and nonspecifically injure endothelium, thereby causing purpura. Clark & Jacobs (93) described experiments in which subpurpurigenic doses of heterologous antiplatelet and antiendothelium sera given together had a synergistic effect and produced purpura. Whether or not endothelial damage

associated with ITP develops as a result of an immunologic reaction remains to be determined, but this sequence does not seem unlikely.

Diseases Produced By Immunization With Tissue Antigens

The following disorders involving the thyroid, central and peripheral nervous systems, testes, uvea, articular tissues, and skin can be produced in animals by immunizing them with autologous, homologous, or heterologous tissue homogenates or extracts, preferably in Freund's adjuvant (1). Regardless of whether auto-, homo-, or heteroimmunization is employed, it is likely that in the pathogenesis of the resulting disease the host's own tissues serve as target antigens and are injured as a result of the immune response. Only rarely do comparable diseases develop in humans as a result of immunization with tissue antigens, as in the case of paralysis developing after the Pasteur treatment for rabies. That these diseases produced primarily in animals should be included in a review of human autoimmune diseases is justified by the fact that they resemble clinically and pathologically to greater or lesser degree certain human diseases of unknown, but long-suspected immunologic origin. On the basis of this resemblance between the laboratory-induced animal disease and that occurring spontaneously in the human, the autoimmune pathogenesis which appears likely to exist in animals has been postulated to operate in such human diseases as thyroiditis, Hashimoto's disease, demyelinating diseases, and sympathetic ophthalmitis. The evidence supporting an autoimmune pathogenesis of these human diseases cannot be as definitive as that available for the autoimmune hematologic diseases for two reasons. First, since the disease in almost all instances is produced in animals, it is necessary to assume an identity between the experimental entity in the animals and the human disease on the basis of a clinical and pathological comparison which can never be entirely satisfactory. Second, while an autoimmune pathogenesis for these experimental diseases seems a virtual certainty on the basis of the method by which they are produced, final demonstration of the responsible immunologic agent or mechanism is still lacking. Attempts to transfer these diseases passively by means of either cells or serum of the affected animal have not been successful. This failure, however, does not rule out a possible role for circulating antibodies since even if circulating antibodies were mediating these diseases, their concentration in the serum might not be sufficient to allow passive transfer because the antibodies might be removed from the blood by the target tissue as rapidly as they were formed. While detectable circulating antibodies or cellular or delayed sensitivity, or both, may develop during the course of experimental auto- or homoimmunization to tissue antigens, there is no conclusive evidence that either of these immunologic responses is the cause of the associated disease.

With these reservations in mind it seems fair to look to this growing group of experimental diseases with some hope of adding to our knowledge of human disease. While our understanding of the pathogenesis of these

diseases is far from complete, improvements in methods of immunization are extending the list of tissues known to be potentially autoantigenic. This suggests the possibility that most, if not all, tissues may keep autoantigenic skeletons in their closets which, with proper methods, may be released in the unsuspecting host. While in the present state of our knowledge it is difficult and perhaps dangerous to force the comparison of these animal and apparently related human diseases too far, the concept that under certain conditions many tissues can be autoantigenic seems worthwhile and should be tested and developed until its true dimensions in human medicine are determined.

Thyroid.—That the thyroid has a peculiar antigen not shown by other tissues of the body but which is very similar from species to species has been well demonstrated (94, 95, 96). Immunization of animals to heterologous thyroid extract or thyroglobulin is readily achieved, sometimes with associated alteration of the immunized animal's own thyroid function (97). More recently Witebsky and his co-workers (98, 99, 100) have been able to immunize rabbits, dogs, and guinea pigs with homologous, or in some instances autologous, thyroid extracts or thyroglobulin. For this purpose the thyroid antigens proved more effective if they were given in complete Freund adjuvant, although this was not absolutely necessary. Rabbits injected with homologous or autologous thyroid showed antithyroid antibodies detectable by complement fixation, precipitation, or hemagglutination of tanned cells (101). No significant reaction could be detected between these antithyroid sera and other homologous tissues or cells (98). In rabbits immunized with rabbit thyroid there was a decrease in the detectable thyroid antigen of their thyroid glands. This presumably was caused by a combination of circulating antithyroid antibody with thyroid gland antigen which eliminated or neutralized the antigen (99). In both dogs and guinea pigs, detection of circulating antithyroid antibodies was also possible after immunization with homologous thyroid (100). One possible explanation for the autoantigenicity of thyroid is that the effective antigen, thyroglobulin, normally exists only in the thyroid colloid, therefore is not released into the blood stream as such and might be considered essentially foreign to the rest of the organism.

In addition to forming detectable circulating antithyroid antibodies, the rabbits, guinea pigs, and dogs immunized with homologous thyroid developed marked inflammatory and degenerative changes in their thyroids presumably as a result of the action of antithyroid antibodies (100). These changes consisted of (*a*) infiltration of lymphocytes, eosinophils, and plasma cells about and occasionally in the follicles; (*b*) occasional development of lymphoid follicles with reaction centers; (*c*) fibrosis of stroma; (*d*) reduction in size of acini and thinning of acinar colloid; (*e*) variation of acinar epithelium from columnar to flattened with occasional mitoses in some areas and degeneration in others; (*f*) in advanced examples virtually complete replacement of thyroid by fibrous tissue and

inflammatory cells. The histologic changes could not be regularly correlated with the amount of circulating antibody, particularly in the dogs and guinea pigs. Nor could histologic changes be produced by passive transfer of serum from affected animals. However, a correlation between circulating antibody and morphologic changes need not be expected since there was no evidence that the particular antibody measured in the serum was responsible for the tissue changes.

Since the histologic picture of the thyroids of these animals bears a strong resemblance to that of thyroiditis in the human, evidence of an autoimmune process has been looked for in patients with thyroiditis and other thyroid diseases. Roitt *et al.* (102), observed that patients with Hashimoto's disease had high serum gamma globulin levels which returned to normal within six months after removal of the thyroid. They were also found to have precipitating antibodies to normal human thyroid extract and to human thyroglobulin but not to other human tissues. Witebsky and his associates (100) found circulating antibodies to human thyroid extract in 12 patients with chronic thyroiditis. These antibodies were regularly detected by the tanned cell hemagglutination technique and in one case by complement fixation and precipitation. Six other patients with biopsy-proved chronic thyroiditis, several patients with other thyroid diseases, and 120 patients with nonthyroid diseases had no demonstrable antithyroid antibodies. The thyroids of the 12 patients having antibody showed varying degrees of lymphocytic and plasmacytic infiltration and follicle formation, fibrosis, foreign body giant cell reaction to colloid, granulomatous reaction and reduction in acinar size and colloid content—the usual changes of nonspecific thyroiditis and Riedel's struma.

In human thyroiditis, the evidence of an autoimmune pathogenesis is strong: first, because of the close morphologic resemblances between human and animal diseases; second, the antigen, thyroglobulin, has been isolated; and finally, because, in both human and animal disease, circulating antibody can be detected. However, the nature of the autoimmune mechanism is still unknown. There is no evidence to prove that the antithyroid antibody found in either animals or humans is causing the disease. Participation of a delayed or cellular sensitivity in this situation has not been ruled out and certainly must be considered.

Central nervous system.—Destructive demyelinating and inflammatory lesions in the central nervous system (CNS), experimental allergic encephalomyelitis (EAE), have been experimentally produced in monkeys, dogs, rabbits, guinea pigs, rats, and mice by immunization with heterologous, homologous, and even autologous CNS tissue. This phenomenon was first reported by Rivers and co-workers (103, 104, 105) who produced it in monkeys (103, 105) and rabbits (104) only after many injections of homologous or heterologous brain. Later workers took advantage of the antigen-potentiating effect of Freund's adjuvant (1) and were able to produce such lesions after a single or a few injections of CNS in complete

adjuvant (106 to 116). The acid-fast bacilli in the adjuvant appeared to play an essential role in this rapid immunization. The nature of the antigen apparently shared by the CNS of many species was first indicated by Schwentker & Rivers (104) who found it most concentrated in the white matter and absent in the newborn brain. The antigen was found to appear in the brain at the same stage of development as did myelin [Kabat, Wolf & Bezer (109)]. These observations plus the fact that the autoimmune response produced destruction of myelin strongly suggested that the antigen was related to myelin. Tal & Olitsky (117) and Waksman *et al.* (118) implicated proteolipides of the brain as the probable antigens producing immunization. Proteolipides as described by Folch & Lees (119) are lipoproteins insoluble in water and soluble in chloroform-methanol-water mixtures which are found in almost all tissues but are most concentrated in the white matter of the brain.

The response of animals to the CNS antigens may be manifest by destructive lesions in the CNS, by circulating complement-fixing antibrain antibodies, and by delayed type cutaneous sensitivity to brain. The simultaneous development of circulating antibodies and delayed sensitivity with the morphologic changes in the CNS would seem to imply an immunologic pathogenesis for these changes. However, it was found impossible to induce lesions of the CNS by transfer of serum (106 to 111), nor did levels of circulating antibrain antibodies correlate with the degree of CNS damage (111, 113, 120). The absence from the serum of the antibody responsible for the CNS damage, however, might well be explained by the antibody being taken out of the circulation by the target tissue as rapidly as it was formed (106). Since the brain preparation used for immunization was obviously a complex mixture of antigens calling forth multiple antibody responses (120), it was entirely possible that the complement-fixing antibody detected in the serum might be unrelated to an antibody reacting with the CNS tissue. The development of delayed cutaneous sensitivity to CNS antigen in animals immunized with CNS was observed by Freund, Stern, & Pisani (108) and by Waksman and his associates (110, 121), and was thought to correlate with the development and extent of the EAE (118, 121). However, attempts to passively transfer the disease with cellular exudates from affected monkeys were unsuccessful (109), indicating that the pathogenetic mechanism was not the same as that in tuberculin hypersensitivity. Successful transfer of EAE was obtained by Lipton & Freund (122) who joined normal rats and immunized rats in parabiosis and found that about one-half of the normal rats joined to rats with EAE developed the disease. In this situation transfer of cells and serum plus the possible transfer of antigen made interpretation in terms of pathogenesis difficult.

Several additional observations on the development of EAE suggest, but by no means prove, the immunologic nature of the disease. Kabat, Wolf & Bezer (123) found that cortisone administered to immunized monkeys prevented the local granulomatous response to the adjuvant depot and also

the development of EAE. Lee & Olitsky (124) showed that in mice EAE, like many other allergic phenomena, is enhanced by pretreatment with H. pertussis vaccine. In addition, these workers showed that a strain of mice susceptible to EAE was also susceptible to foreign serum-induced anaphylaxis, while a strain resistant to EAE was also resistant to anaphylaxis (125). The difference in susceptibility to anaphylaxis of these two strains was not correlated with the amount of antibody formed against the antigen used to induce anaphylaxis or with their antibody-forming capacity in general but presumably with other characteristics determining tissue response to immune reactions.

The morphologic manifestations of EAE have shown minor variations probably related to the duration of the process from species to species, and from one observation to another within a species. The monkey can be taken as a prototype. Within a few weeks after injection of brain in adjuvant grossly visible focal disseminated lesions developed in all parts of the brain, most frequently in the white matter especially about the ventricles (105, 106, 107, 126). These lesions characteristically were related to small veins or capillaries. Occasionally they extended into the grey matter, but peripheral nerves were spared. In the early lesions neutrophilic and eosinophilic polymorphonuclear leukocytes, fibrin, and sometimes hemorrhages were found about involved vessels. Within a few days these granulocytes were replaced by lymphocytes, monocytes, plasma cells, and proliferating microglial cells. In the inflammatory lesions there was focal perivascular degeneration of myelin with a relative sparing of the axis cylinders. In spite of the perivascular location of these rather intense inflammatory reactions, the vessels remained patent and intact. With progression of the diseases large numbers of mononuclear cells and occasional giant cells gathered or formed in and about the lesions. The late inactive lesions consisted of focal demyelination with preservation of most of the axis cylinders, prominent microglial phagocytes and a mild to moderate astrocytosis. Lesions of varying ages were usually present together. In addition to the lesions in the substance of the brain there was a variable infiltration of both acute and chronic inflammatory cells in the leptomeninges.

In the guinea pig where the morphologic picture of EAE may differ slightly from that in the other species, Freund, Stern & Pisani (108) found a diffuse mononuclear infiltration of meninges. The meningeal vessels had acute hyaline and leukocytic thrombi with leukocytic infiltration of vessel walls and perivascular spaces. The lesions in the brain resembled the vascular lesions of the meninges with an additional astrocytic gliosis and little evidence of demyelination. The roots of the spinal nerves also showed a similar involvement. The conspicuous vascular changes in the guinea pigs led these workers to postulate that much of the tissue damage resulted from vascular injury. Employing a modified adjuvant, Freund, Lipton & Morrison (114) produced a more chronic demyelinating disease in guinea pigs similar to that described in the monkey. Lumsden (110) was

impressed with the response of the mesenchymal cells of the guinea pig brain in EAE. He found that most of the chronic inflammatory cells developed from proliferating adventitial cells and microglia with a minor contribution of hematogenous cells.

The relationship of EAE to the human demyelinating diseases cannot be determined with certainty. It is based largely on morphologic evidence, except in the case of the infrequent postPasteur treatment paralysis in which the genesis of the human disease is comparable to that in EAE. Such evidence, which necessitates comparison of tissue reactions from one species to another, is always difficult to interpret. However, on the basis of morphologic study most workers feel there is a reasonable correspondence between EAE and acute disseminated encephalomyelitis, seen as an occasional sequela of measles, small pox, chicken pox, mumps, influenza and rabies or small pox vaccination, and acute and subacute necrotizing encephalomyelopathy (106, 110, 126, 127). The most evident difference between EAE and these human diseases is the more violent and extensive inflammatory reaction in brain and meninges in EAE. This severe, acute inflammatory component resembles in some respects the Arthus reaction which can be induced in the brain (106). However, one explanation for the more marked acute reaction seen in EAE may be that it is often studied histologically at an earlier stage than are the human diseases. The relationship of EAE to multiple sclerosis is not so evident on histologic grounds (110, 114). However, several observers (106, 127, 128) feel that a fair similarity exists between the lesions of multiple sclerosis and of the more chronic forms of EAE. The relationship between EAE and these human diseases and the question of whether autoimmunization plays a role in human demyelinating diseases remain uncertain, but much evidence supports their likelihood.

Peripheral nervous system.—In the course of work on EAE, several observers found lesions in the peripheral nerves associated with the CNS diseases (108, 110, 129, 130). However, such lesions were not always present after immunization with CNS antigen (107, 109) and when found they were often not as numerous or extensive as the lesions in the CNS. Demyelinating lesions of the peripheral nerves were produced with regularity and at times exclusive of CNS lesions by immunization with heterologous or homologous peripheral nerve antigens. Waksman & Adams (131, 132) produced experimental allergic neuritis (EAN) in rabbits, guinea pigs, and mice by immunization with heterologous or homologous peripheral nerve emulsion in Freund adjuvant. Within 2 to 2½ weeks the disease developed exclusively within the peripheral nerves of the rabbits and mice and in the peripheral nerves plus the CNS of two-thirds of the guinea pigs. This distribution of lesions in rabbits and mice strongly suggests that in these species there is a peripheral nerve antigen distinct from the CNS antigens. Complement-fixing antibody and skin reactions of mixed Arthus and tuberculin type to the injected antigen appeared but could not be correlated with the severity of the disease. The lesions in all three species were

similar and no difference was noted between immunizations with homologous or heterologous nerve. The most common site of involvement was the spinal ganglion, then the dorsal roots, the ventral roots, and finally the peripheral nerves. In all these sites the lesions consisted of focal perivascular demyelination with limited injury to or destruction of axis cylinders. There was an infiltration of histiocytes and lymphocytes with phagocytosis of the altered myelin. In the spinal ganglion in severe cases there was loss of some of the ganglion cells. In the peripheral nerves the lesions varied in size involving amounts ranging from a few fibers of the nerve to its entire thickness. In rabbits and mice the nerve sheaths were uninvolved while perineural inflammatory infiltrates developed in the guinea pigs.

The course and morphologic alterations of EAN bear certain resemblance to acute infectious polyneuritis, the Guillain-Barré syndrome, and Landry's paralysis, which are felt to be a single category by Haymaker & Kernohan (133). The major differences between the experimental and human diseases are the greater destruction of axis cylinders and ganglion cells, the lack of perivascular arrangement of lesions, and the more progressive course of the human disease. Whether, in spite of these differences, the two processes are similar and whether an autoimmune pathogenesis operates in the human diseases are questions that remain to be answered.

Testes.—The antigenicity of homologous sperm has long been recognized [Metchnikoff (134)] but only recently has testicular damage been associated with the immune response to testicular antigens [Freund, Lipton & Thompson (135, 136, 137)]. Lewis (138) concluded that testis and brain possessed a common antigen or similar antigens when he found that rabbit antisera against brain fixed complement in the presence of testicular extracts. This antigenic relationship was not sufficient, however, to cause damage to the testes in animals immunized with brain, or to cause damage to the brain in animals immunized with testes [Lumdsen (110)]. Voisin *et al.* (139) noted injury to the testes of guinea pigs immunized with homologous testes in Freund adjuvant, but since they also found testicular changes in animals immunized with other tissues they ascribed the testicular injury to nonspecific stress.

Freund and his colleagues (135, 136, 137) injected homologous or autologous testes or sperm in complete adjuvant into guinea pigs and rats and noted an autoimmune response manifested by complement-fixing, sperm-immobilizing, and antihyaluronidase antibodies, delayed cutaneous sensitivity, and aspermatogenesis. The effective antigen was found only in homologous and not in heterologous testes and was present in a mitochondrial fraction of testis, in washed sperm, and in a polysaccharide-like extract of testis. The levels of complement-fixing antibody and the development of delayed skin sensitivity roughly paralleled the degree of testicular damage, while the levels of anaphylactogenic, sperm-immobilizing, and antihyaluronidase antibodies bore no relation to it. Testicular damage was not transferrable with large amounts of serum from immunized guinea pigs.

The morphologic alteration was found almost exclusively in the spermatogenic cells. The earliest change was a reduction in number of mature sperm and the appearance of immature sperm in the tubular lumens. Later there was absence of sperm and degeneration and exfoliation of spermatogenic cells down to and including spermatogonia. Finally, all spermatogenic cells were lost and Sertoli cells were left lining the tubules which contained acellular amorphous eosinophilic material. The interstitial cells and connective tissue of the testis were unaltered except for occasional foci of mononuclear infiltration and fibrosis about affected tubules. Other tissues of the body including the epididymis and prostate were not affected. The relative lack of inflammatory reaction in this disorder sets it apart from the other presumably autoimmune reactions to tissues. It was postulated that the absence of inflammation might be due to the elimination of injured cells via tubules, epididymis, etc., so that they never or only rarely came in contact with the vascularized connective tissues. Regardless of the reasons, it would seem that the immunization with testicular antigens results in a primary destruction of germinal cells not necessarily mediated by inflammatory cells of any kind. This suggests that the characteristic mononuclear infiltration about most destructive immunologic reactions may be a secondary process and not necessarily the agent of tissue destruction.

The relationship of this mechanism of inducing aspermatogenesis to human male infertility is not known. It might, however, play a role especially after trauma to the testis which causes extravasation of sperm and the formation of spermatogenic granulomas which are similar in many respects to the granulomas forming about depots of Freund adjuvant.

Uvea.—The injection of homologous uvea with complete Freund adjuvant in guinea pigs and monkeys produced an inflammatory reaction in the uvea of a great proportion of the animals [Collins (140, 141)]. The reactions were characterized by focal infiltrations of lymphocytes and epithelioid cells in the uvea and by nodules of proliferating reactive pigmented epithelial cells invaded by macrophages. In immunized animals trauma to the iris precipitated a reaction in the traumatized eye. No information is available concerning antibody response or development of cutaneous sensitivity to the uvea antigen, but the timing and tissue specificity of the reaction suggest an underlying autoimmunization.

This experimental lesion closely resembles that of sympathetic ophthalmia of man, long thought to be caused by an autoimmune response to the antigens of an injured eye. This suspicion is based upon (*a*) the interval usually existing between injury to an eye and development of the sympathetic lesion; (*b*) the fact that uveal pigment will serve as an antigen and frequently elicit positive skin tests in patients with the disease; and (*c*) the histologic appearance of the lesion which suggests a reaction of eosinophils, lymphocytes, and other mononuclear cells to uveal pigment.

Articular tissues.—Recently Pearson (142) has reported the production of an extensive polyarthritis in rats given repeated injections of macerated

homologous muscle in complete Freund adjuvant. The arthritis most frequently involved the ankles and tarsal joints, making them red and swollen and causing exudation of serum. The active process receded gradually over a period of weeks or months leaving behind permanent arthritic residuals including ankylosis. Histologically, there was an intense inflammatory reaction of the articular tissues. There was early edema and fibroblastic proliferation with relatively little inflammatory infiltrate. Proliferation of periosteal osteoblasts with new bone formation and an invasion of tendon sheaths and joint space by granulation tissues resulted in considerable bony deformity and pannus formation. The reaction was limited to the region of the joint but did include local infiltration of skeletal muscles and blood vessels by lymphocytes and monocytes. If this disorder can be established with some degree of certainty as an autoimmune reaction, it may be an important development in our understanding of rheumatoid diseases.

Skin.—In the course of studies on the possible role of antibodies in homograft rejection Voisin & Maurer (143) noticed that rabbits injected with homologous skin in Freund adjuvant developed an atrophy of the skin and alopecia. This preliminary and as yet unconfirmed experimental observation is mentioned primarily to indicate the variety of tissues that may prove to be capable of eliciting destructive autoimmune responses.

Kidney.—On the basis of clinical observations glomerulonephritis has been thought by some to be an autoimmunologic disorder. However, in spite of much experimental work no convincing demonstration of an autoimmunologic pathogenesis has been obtained. While heteroimmune nephrotoxic serum nephritis, an immunologic model for the study of glomerulonephritis, is understood in considerable detail, the method of producing the disease, i.e., the injection of heterologous antitissue antibodies, does not help greatly in our understanding of the immunologic processes, if any, involved in pathogenesis of human glomerulonephritis. The fact that the morphologic changes in nephrotoxic serum nephritis resemble those in human glomerulonephritis may attest more to the limited variety of histologic responses of the kidney than to a similarity of pathogenesis in the two conditions. Almost all attempts to induce an autoimmune response to kidney in various laboratory animals utilizing either heterologous or homologous tissue have been unsuccessful. Even the use of Freund's adjuvants which have brought out the antigenic best in most tissues has not enabled anyone to demonstrate an autoimmune response to kidney antigens. One exception to this series of failures was the observation by the Caveltis (144, 145, 146) that in rats injections of mixtures of homologous or autologous kidney and killed beta hemolytic streptococci produced morphological and functional renal changes suggestive of glomerulonephritis. Circulating antibodies to the injected antigens were also demonstrable. Numerous attempts to repeat this observation plus variations on this experimental theme have been unsuccessful, and it still awaits confirmation. However, in view of the clinical characteristics of glomerulonephritis and the demonstrated autoantigenic potenti-

alities of a number of other tissues it seems possible that the necessary conditions for demonstrating autoantigenic properties of kidney might be forthcoming. Such an experimental demonstration would offer a plausible immunologic mechanism for the pathogenesis of glomerulonephritis.

Lens.—The lens of the eye possesses characteristic antigens which are not found in other tissues but which are common to the lenses of several species [Halbert *et al.* (147)]. These antigens induce antibody responses when injected with Freund's adjuvants into homologous hosts (136, 148). In these immunized animals antilens antibodies are present in both serum and the aqueous humor but no morphologic alteration in lens or eye can be found. Offspring of animals with antilens antibodies show no significant changes in the eye, indicating that the lens of the eye apparently develops normally in the presence of transferred maternal antilens antibody. In this situation it would appear that the production of antibodies capable of reacting with tissue antigens of the host, i.e., autoimmunity, is not associated with any morphologic change or disease. Whether this is because the structure of the lens is impervious to antibody, or whether the response to lens antigens includes only the production of circulating antibody and not tissue destructive responses remains to be seen.

Diseases Associated With an Affinity of the Host's Gamma Globulin for Certain Tissue Constituents

In a number of human diseases evidence of an affinity of the host's gamma globulin for various tissues has been obtained. Two major questions arise concerning these observations: first, is this affinity based on a real antigen-antibody reaction or could the serum be exhibiting some nonimmunologic reactivity; and second, of what consequence is this reaction in the over-all development of the disease?

Cavelti's (149) report of antihuman heart antibodies in the sera of 75 per cent of patients with active rheumatic fever has gone unconfirmed and is therefore difficult to evaluate. There is little, if any, additional evidence which specifically implicates autoimmune mechanisms in rheumatic fever. Recently Gajdusek (150) has reported a complement-fixing reaction between the gamma globulin of some patients with disseminated lupus erythematosus (DLE), lupoid hepatitis, chronic hepatitis and macroglobulinemia, and normal tissue antigens. Nine of 11 patients with DLE, three of four with lupoid hepatitis, 11 of 25 with chronic hepatitis, and two of five with macroglobulinemia showed a significant complement-fixing reaction with human liver while only 2 to 5 per cent of normals or patients with other diseases showed such a reaction. These reactions were not tissue or species-specific, but were equally strong against human liver, kidney and muscle, and rat liver and kidney. In support of the immunologic character of these reactions it can be said that the active part of the serum is the gamma globulin, that the activity is stable at 56°C. and destroyed above 60°C., that there are prozones in the antigen titrations, and that the reaction

fixes complement. The cross reactions of the sera of these patients with various tissues from members of the same or even different species are quite similar to the cross reactions demonstrated by rabbit and guinea pig antisera to human liver or kidney. There was nothing in the histories of these patients to suggest either a viral infection or chemical sensitization by which the patients' tissues might have been rendered autoantigenic.

Working along this same line, Mackay, Larkin & Burnet (151) tested the complement-fixing reaction of the sera of two patients with macroglobulinemia and DLE against their own tissue antigens and against tissue antigens of other individuals. In both instances the sera did not react with the tissues from the same host but did react with the tissues from other patients. In order to explain the formation of globulins capable of reacting with the host's tissues these authors postulated a mutation in the host's mesenchymal cells with these altered cells then playing a dominant role in the host's immunologic responses. This mutation of mesenchymal cells would involve (*a*) loss of recognition units so that normal body constituents could act as antigens, and (*b*) formation of antibody or gamma globulin of varied nature, some of which could by chance combine with tissue of other individuals. Whatever the explanation, on the basis of these observations it would appear that such patients make a spectrum of gamma globulins potentially capable of reacting with various tissue constituents, and that the antigenic characteristics of these tissue constituents differ from individual to individual. What role these globulins capable of reacting with tissues play in the pathogenesis of the various diseases remains to be seen. Certainly, there are no obvious morphologic changes common to all these disease entities which might be attributed to this single mechanism.

Studies of the so-called LE factor in the serum of patients with DLE suggest that it reacts in a rather specific way with nuclear material from diverse sources. On the basis of staining reactions of the lupus cell inclusion [Hargraves, Richmond & Morton (152)] and from the observations of Miescher & Fauconnet (153) which demonstrated the adsorption of LE factor to isolated nuclei, the reaction between factor and nuclei seems clear. Further work by Holman & Kunkel (154) has shown that the LE factor reacted with nucleoprotein. Both these workers and Seligmann (155) showed that the factor reacted with DNA but not with RNA. The source of DNA was not important since serum from lupus patients would react with DNA from human leukocytes, beef thymus, pneumococccus, or bacteriophage to form a precipitate (155). Immunohistochemical study of the LE cell inclusions and free bodies shows them to be coated with gamma globulin, confirming the above observations (154, 156, 157). Whether this reaction between LE factor and nuclear material is immunologic remains to be determined. Also still unclear is its relationship to the postulated enzymatic changes involving the inactivation of the intracellular deoxyribonuclease inhibitor which permits intracellular deoxyribonuclease to act upon the nucleus giving the characteristic LE body [Kurnick *et al.* (158, 159)].

In DLE we have some indication that the presence of the LE factor per se may not be particularly important in the pathogenesis of the disease. First, the presence of the LE factor in the blood of patients with DLE cannot always be correlated with the activity of the disease. Second, and more striking, is the demonstration of the LE factor in the blood of otherwise entirely normal babies born of mothers with DLE (160, 161). If the situation in DLE can be taken as an example, it may well be that serum globulins capable of reacting with the host's tissues may not always be the vital element in the diseases in which they are found, but rather perhaps merely one of a number of reflections of incidentally altered metabolism in the diseased host.

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NEOPLASTIC DISEASES (CANCER)[1]

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This review of neoplastic diseases is an attempt to describe developments of the past two years. The reviewer has chosen to discuss only cancer in man with the specific purpose of presenting some aspects of the natural history of cancer. Extrapolation to man of the results of recent *in vitro* and animal studies has been deliberately avoided, with one major exception.

General Effects of Tumors Upon The Patient

Recent *Annual Reviews of Medicine* (1, 2, 3) have called attention to the effects of tumor growth upon the metabolism of the patient. Such remote effects, metabolic and others, could result either from the elaboration of a "toxic" product by the tumor, or the removal by the tumor of substances required for normal metabolism of the patient. Chemical products as illustrations of remote effects are discussed in a later section; immediately following are those instances in which no chemical product of the tumor has been identified, and the remote effect, by default, may be thought to depend upon the capacity of the tumor to segregate essential metabolites in defiance of the usual homeostatic controls.

Effects presumably following segregation of metabolites.—Cachexia and negative nitrogen and phosphorus balances resulting from advanced cancer have been studied for the response to forced feeding. Although weight gain, and positive nitrogen and phosphorus balances, were induced (4), host repletion could not be sustained. Transient clinical benefit was seen in some patients, but in half there was a detrimental effect. These observations support the impression of increased caloric expenditure in some cancer patients, and this may be related to the behavior of the tumor as a "nitrogen trap" with resultant rapid breakdown of normal tissues to supply specific protein precursors. An alternative explanation of the increased energy expenditure during forced feeding is the necessity for the patient to burn more food plus the induced speeding up of tumor growth rate. In a comparison of cachexia in patients with and without cancer (5), forced feeding resulted in weight gain in both, but with a striking failure of albumin regeneration in the cancer patients. A study of one patient with chronic myeloid leukemia using C^{14} glycine showed no abnormality of half-life of serum albumin and globulin (6). The consistent appearance of hyperglobulinemia and hypoalbuminemia in patients with cancer is again documented (7); disappearance of alpha lipoprotein was shown as more advanced tumors were studied. Occasionally neoplasms are associated with inability to make gamma globulin (8, 9). Abnormal proteins such as cryoproteins were

[1] The survey of literature pertaining to this review was concluded on July 1, 1957.

demonstrated in association with nonmyelomatous tumors such as lymphoma (10), neoplasms of the breast (11), or lung (12). Thrombophlebitis migrans occurred in the latter, and in other instances bleeding resulted (13). In one patient bleeding was associated with a cryoprecipitable complex consisting of fibrinogen and gamma globulin, with reduction in fibrinogen and prothrombin activities (14). A hemorrhagic diathesis has been seen occasionally in association with cancer of the prostate and other tumors. In some instances, low fibrinogen due to a proteolysin is at fault (15); in others both proteolysis of fibrinogen and intravascular coagulation are responsible (16); and in one patient careful analysis could find no simple explanation of the clotting defect (17). Another defect in the clotting mechanism of cancer patients is a tendency to the formation of multiple thromboses. These occur in many veins (18, 19, 20), in capillaries of the viscera, and on heart valves (21), in association particularly with cancer of the pancreas, but also with many other tumors. The relationship to cancer of nonbacterial thrombotic endocarditis with vegetations on the mitral and aortic valves, and consequent embolism (22) has been postulated. In a study of 78 patients with these lesions at autopsy, 36 per cent were associated with cancer (23). It was suggested that fibro-collagenous degeneration of the valve leaflet occurs, followed by deposition of thrombi.

The failure of the patient with cancer to maintain the ordinary body defenses is also seen in relation to infection. Infections in leukemia apparently related to lack of granulocytes are commonplace. The patient with Hodgkin's disease has also been known to have an altered host resistance to infection. Loss of many types of delayed allergic reactivity without impairment of circulating antibody response has been restudied with bacterial, viral, treponemal, and fungal antigens (24) and with a simple chemical (25). The relation of this skin anergy to resistance to infection is unknown, but patients with Hodgkin's and other lymphomas not only develop tuberculosis but also cryptococcosis (26 to 30), histoplasmosis (31), and occasionally mucormycosis (32).

Anemia is another common concomitant of cancer. In one study (33), hemorrhage and infection could not account for 33 per cent of anemia in cancer patients. Of the anemias not related to the above causes, Miller and his colleagues (34) found that 9 of 38 patients had deficient erythrocyte production, and in four of these, no marrow metastases were demonstrated. Twenty-nine of the 38 patients with anemia had normal or increased production of red cells, and 13 of these were shown to have increased rate of destruction. Similar findings are reported by Hyman & Harvey (35), who also have shown that in some instances the rapid rate of destruction is caused not by any defect of the red cell, but more likely by a hemolytic plasma factor (36). A hint as to the nature of this factor is perhaps found in the demonstration of a potent hemolysin and agglutinin in extracts of leukemic white cells (37).

Disturbances of carbohydrate metabolism have been noted in patients

with cancer. Diabetic types of glucose tolerance were noted in 37 per cent and diabetes in 13 per cent of 950 patients with neoplasia (38). Marks & Bishop (39) described a decreased rate of disappearance of infused glucose in cancer patients as compared to controls. The mechanism of this is not understood, but latent diabetes and starvation have been excluded. Hypoglycemia because of cancer has been reported especially in association with large retroperitoneal spindle-cell sarcomas (40 to 43). Hypoglycemia in patients with cancer of the liver has been studied (44). It apparently was not caused by liver destruction, but was associated with segregation of large amounts of glycogen in the tumor.

Hypercalcemia is one of the common metabolic disturbances which arises from metastatic cancer of bone. General reviews have been published (45, 46). Occasionally differentiation from hyperparathyroidism is difficult (47). Hypercalcemia also occurred in cancer patients in the absence of demonstrable metastases (48, 49, 50) and, in some instances, disappeared with removal of the tumor. Extracts of such tumors have not yielded a calcium mobilizing factor (50).

A number of specific organ dysfunctions have been described in cancer patients in the absence of metastases, and are perhaps other examples of the remote effects of the tumor upon the host. Such occurs in the nervous system of patients with tumors, according to reports of degeneration of the cerebellum (51, 52) and cord (53). Wells & Silver (54) noted neurologic manifestations in 22 of 42 patients with acute leukemia. At autopsy, leukemic infiltration or hemorrhage into cord, brain, or peripheral nerves accounted for a majority but by no means all of the signs and symptoms. Peripheral neuritis has been described with myeloma (55) and other tumors (56).

The enlargement of the liver in leukemia sometimes results not from infiltrate but from increase in the volume of the individual hepatic cells (57). A similar situation occurs in the kidneys of patients with leukemia, where 43 per cent of the kidneys without infiltration showed significant enlargement (58). No histologic correlate or characteristic clinical picture was noted. In mutliple myeloma the adult Fanconi syndrome has been described (59). Renal failure because of melanin from a melanoma, without kidney metastases, has been noted (60). Sandberg *et al.* (61) studied values for serum and urine uric acid in the different types of leukemia. The patients with acute lymphocytic leukemia had the most marked elevations. Uric acid pools were normal, borderline, and elevated in three patients with chronic leukemia but turnover rates were normal (62). Finally, 24 cases are described (63, 64) of fulminating peptic ulceration in association with tumors of the pancreas. These resemble islet tumors but do not secrete insulin and are frequently malignant. The patients showed excessive formation of gastric juice and atypically placed peptic ulcers. An analogous situation has been noted with familial adenomatosis of the endocrine glands (65).

Effects caused by chemical products of tumors.—The mechanisms by which the effects of tumors are exerted upon patients are not in all instances mysterious and speculative. Certain tumors manufacture chemical products which can be identified and measured. In some instances, the substance produced and its metabolites provide a relatively complete understanding of the consequent clinical syndrome, but the significance to cancer research is somewhat greater. For many of these tumors the diagnosis can be quickly confirmed by demonstration of the product. The 24-hr. output and serum concentration can, in some instances, be used as an objective and direct measure of rates of tumor growth and the success of therapy. Finally, these tumors, though uncommon, may provide clues to a more general understanding of the physiology and biochemistry of abnormal growth. Many such tumors are of endocrine origin, and not all of these can be discussed. The reviewer has chosen a few instances to illustrate new information on substances produced by neoplasms.

The brilliant observation of Conn on primary aldosteronism is summarized by him in a recent review (66). The clinical features include periodic muscle weakness, intermittent tetany and paresthesias, polyuria, hypertension, hypokalemia, hypernatremia, alkalosis, and renal damage. Diabetes mellitus occasionally is found (67). The primary disease is seen in association with adenomas (68), adrenocortical hyperplasia (69), adrenal cortical cancer (70) and, in one instance, with morphologically normal adrenals (71). Although bilateral adrenalectomy or removal of the adenoma usually cures the disease, hypertension may persist (72). Thus far only a single chemical product, aldosterone, has been identified, but more work is needed (73).

Adrenal cortical tumors producing Cushing's disease have been studied carefully in the last few years. Cope & Raker (74) have summarized experience with 46 patients. The adrenal cortex was involved in every case operated, 44 in all. Of these, 27 patients had hyperplasia, 12 adenoma, and 5 carcinoma. Elevated plasma and urine 17-hydroxy-corticoids, and urine 17-ketosteroids are generally noted in the three forms of the disease, although in some patients with adenomas the urine 17-ketosteroids are normal (75, 76). In hyperplasia, low excretion of compound F was noted (77). It is postulated that in virilism with adrenal hyperplasia there is a deficient conversion of 17-hydroxyprogesterone to hydrocortisone, perhaps due to a deficient hydroxylation mechanism, with routing of these partially hydroxylated precursors into androgens (78). A variety of steroid metabolites have been found in adrenal cortical cancer (79). Hertz and his colleagues (80) have developed an interesting drug called amphenone, which inhibits the output of glucocorticoids in animals and in patients with adrenal cortical cancer (81).

The problem of pheochromocytoma has been reviewed (82); of 51 cases, 16 per cent were malignant. The presence of catechols in the urine has been studied by a number of investigators. The metabolites so far identified in

the urine of patients with adrenal pheochromocytoma have been epinephrine, norepinephrine (83), and 3-hydroxytyramine (84); 3-4-dihydroxyphenylalanine has been noted in the tumor (84). Epinephrine has at times been absent from the urine and an unidentified metabolite of norepinephrine noted (85). Tumors of the paraganglionic tissues produced norepinephrine (86) and 3-hydroxytyramine (87), but not epinephrine (88).

The original suggestion of Isler & Hedinger (89) of the carcinoid syndrome, and the formal recognition and definition of its chemical basis by Thorson, Waldenström and their co-workers (90, 91), have been followed by many related observations. The syndrome appears in patients with hepatic metastases from malignant argentaffinoma and consists of attacks of flushing, diarrhea, asthma, and development of organic heart disease in association with a high tumor and plasma content of serotonin (92, 93, 94). Sjoerdsma and his colleagues (92) have shown an increase in 5-hydroxyindole acetic acid (5HIAA), a metabolite of serotonin, in the urine. They also found that 60 per cent of administered tryptophan appeared in the urinary 5HIAA (95). These authors suggest that some of the manifestations of the syndrome may arise from tryptophan deficiency. In one study (96), 5HIAA was not found elevated in other neoplasms, but in others it was increased in carcinoma of the breast and larynx (97) and bronchus (98). In cancer of the bladder (99) there has been noted an increase of a variety of tryptophan metabolites in the urine. Serotonin and 5HIAA appeared in the urine of patients with cancer of larynx or bronchus after a tryptophan loading dose (100). In another study of various neoplasms, 3-hydroxykynurenine appeared in the urine after giving tryptophan but disappeared when large amounts of pyridoxine were administered, suggesting that availability of the vitamin is a limiting factor in the orderly catabolism of tryptophan (101). Concerning prevalence of the carcinoid syndrome, MacDonald reported (102) an autopsy experience of 356 carcinoids of the gastrointestinal tract, 24 showing metastases, only three of whom had the syndrome. A high prevalence of peptic ulceration and arthritis was also noted. In another autopsy analysis of 8000 patients (103), 26 had carcinoids. Of 16 without metastases, three had endocardial fibrosis; of ten with metastases, seven had endocardial fibrosis. The histology of the cardiac lesion consisted of peculiar fibrous tissue devoid of elastic fibers, present on intact endothelium (104). Large numbers of mast cells were noted. Since mast cells can produce histamine, it is interesting that some of the flushes have resembled histamine reactions, being induced by alcohol (105) and by eating (106, 107). Thorson (108) has made a careful study of the physiologic events during the flush, and Waldenström (109) has demonstrated increased histamine in the urine and blood of five patients with the carcinoid syndrome. Another relationship between histamine and neoplasia has been demonstrated by a number of investigators in a disease associated with urticaria pigmentosa. Recognized as a dermatologic entity due to mast cell accumulations in the skin, it is occasionally associated with a generalized

mast cell invasion of bones, liver, and bone marrow (110 to 113). Not uncommonly there has been the appearance of fulminating "mast cell leukemia" (114, 115). Waldenström (116) has found increased urinary histamine in five patients with urticaria pigmentosa. Hamrin (117) has described one patient with this disease who developed nausea, reddening of the skin, and profound shock after the administration of 0.25 grams of aspirin. Increased histamine and heparin have been found in the liver of a patient dying with mast cell leukemia (115), and chronic hypoprothrombinemia in another (110). A rise in "heparin titer" of the blood has been found after rubbing the skin lesions with a towel (118). 5HIAA has not been found in one patient (119) with urticaria, but both serotonin and 5HIAA were present in extracts of a mast cell tumor of the mouse (120). The physiological aspects of mast cells have been reviewed (121).

Chemical products have been studied in some of the commoner neoplastic diseases. A unique serum protein iodine component has been found associated with physiologically active cancers of the thyroid (122 to 124). Studies on "specific" tartrate-sensitive acid phosphatase produced by prostatic cancer have been reported as showing a better correlation with the presence of the disease than total serum acid phosphatase (125). This is questioned by others (126). Cancer of the breast was shown, in 75 per cent of instances, to be associated with elevation of copper-resistant serum acid phosphatase (127).

Multiple myeloma is associated with chemical products in terms of a variety of abnormal proteins. The abnormal serum proteins (Ms) and the abnormal (Bence Jones) urine protein (Mu) have been the source of considerable speculation concerning their precursor—product relationship. Most of the physicochemical studies have shown that Ms is not the precursor of Mu (128 to 131), but the immunological studies have shown antigenic relationships (132 to 136). The relationship of the carbohydrate moieties of these abnormal proteins to the cross antigenicity is not known, but studies of the carbohydrate fractions of Ms have shown the presence of hexose, hexosamine, fucose, and sialic acid (137). The beta-type myeloma proteins have a higher carbohydrate content than the slower gamma-type abnormal proteins (137, 138). Agreement was not reached in studies of the relationship of cell types to the presence of gamma- and beta-type proteins. (139 to 141). A mouse plasma cell neoplasm was shown to resemble multiple myeloma in man (142). There has been a clear-cut emergence of macroglobulinemia of Waldenström as a specific neoplastic disease, resembling the reticuloendothelioses, characterized by macroglobulinemia, dypsnea, mucous membrane bleeding, and bone marrow infiltration by small atypical lymphocytes (143, 144, 145).

Etiology of Cancer in Man

While the search proceeds for "the" cause of cancer in man, there has over the years appeared unequivocal evidence of a number of causes of

human cancers. Coal tars, distillation products of lubricating oils, ionizing radiation, ultraviolet light, beta-naphthylamine, and arsenic have been associated with a high incidence of cancers of specific sites when man is exposed to them over long periods. In addition, there are a number of agents exposure to which is frequently followed by cancer, although the association is less clear than above. These include ethyl alcohol, tobacco, hematite ores, asbestos, betel nut chewing and manufacture of isopropanol, nickel, chromates, or coal gas. Other disease processes playing a role in the development of cancer are ulcerative colitis, burn scars, *Schistosoma hematobium* infestation, cirrhosis of the liver, postmastectomy lymphatic block, and the Plummer-Vinson syndrome. Whether all of the above are primary and direct causes cannot be proved, but there is no doubt about a systematic and predictable association with the appearance of human cancer.

Carcinogens.—In the last two years new information on industrial carcinogens has been slight. This lack is particularly noted in the American literature. A good review of industrial lung cancer was published (146). Cancer of the lung in hematite miners was reported (147) in 9 per cent of 180 consecutive autopsies. There was no increased radioactivity in the mine. Of 105 deaths occurring among workers in an asbestos works in England, 18 were attributed to cancer of the lung (148) and 15 of these had pulmonary asbestosis. Carcinoma of the lung associated with manufacture of chromates has now appeared in England (149). No new reports are available on the observation of carcinoma of the sinuses occurring in those who manufacture isopropanol (150).

Esophageal cancer was shown to have a strong association with chronic alcoholism in 65 per cent of 84 patients studied (151). Steiner (152) confirmed this in 116 patients with esophageal cancer. There was also a strong smoking history in many of these patients with esophageal cancer. Betel nut cancer of the buccal mucosa was considered to be of complex causation in 650 patients studied; many of the patients also chewed tobacco and had evidence of vitamin deficiencies (153).

The controversy on the relationship between smoking and cancer of the lung continues to be waged and long before this review appears masses of new data and emotionalism will have been presented in the newspapers. The factual evidence as of this time is well presented in an editorial by Clough (154). Steiner (155) pointed out the difficulty in arriving at any interpretation of these data since the entire population is exposed to soots, engine fumes, asphalts, etc., while only half the population are heavy smokers. Kotin (156) also emphasized the role of atmospheric pollution. That there is an urban factor in the increase in lung cancer as well as a tobacco factor seems clear (157, 158). One conclusion must be admitted from almost all the surveys: that the nonsmoker wherever he lives gets far less cancer of the lung than the heavy cigarette smoker. For example, in one study of mortality in England, the death rate from lung cancer for heavy smokers was 20 times that for nonsmokers (159). Tobacco seems similarly

related to carcinoma of the larynx (160), bladder (161), and mouth (162). The whole problem of cancer of the lung, larynx, and urinary tract is summarized by Kennaway (163).

Cancer "caused" or preceded by other diseases.—Cancer as a systematic concomitant of certain diseases has been well-established. In no instance, however, has the precise causative agent or mechanism been identified. Cancer of the mouth, larynx, and esophagus in women with Plummer-Vinson syndrome originally noted in 1936 (164) is documented again in Sweden (160, 162). Cancer of the liver was found in 82 of 2402 patients with cirrhosis autopsied at the Boston City Hospital (165). Seventy-six per cent of the patients with primary cancer of the liver had some type of preceding cirrhosis. Cancer appeared in 13 per cent of patients with healed yellow atrophy of unknown causation, 8 per cent of patients with hemochromatosis and 2.4 per cent of patients with fatty nutritional cirrhosis. There also seemed to be an increase in cancer of the liver in patients without cirrhosis. Other diseases receiving attention were lymphangio-sarcoma following postmastectomy lymphedema (166), and cancer of the colon in chronic ulcerative colitis of childhood (167). In this study, two children of 18 with ulcerative colitis developed cancer of the colon, and in a review of 3070 cases, 72 instances of colon cancer were found.

Three new associations of disease and cancer have been recognized. In 6 of 14 patients suffering from dermatomyositis, cancer of various sites developed (168). Hou (169) has shown an anatomic relationship between the presence of *Clonorchis sinensis* in the bile ducts, and cancer of the bile ducts. Krivit & Good (170) saw five cases of associated mongolism and leukemia. This association had been suspected previously (171, 172, 173). Most of these have had congenital leukemia of the myeloid type. These patients died with diffuse infiltrations of myeloid cells in the viscera. In one survey of 255 older children with mongolism, four developed leukemia (174). The study by Stewart (175) in England on 515 children dying of leukemia showed that 15 of these had mongolism. None of these mothers had received abdominal x-irradiation.

Radiation.—X-irradiation as a cancer-inciting agent in man has been known since the first publication of a case of cancer of the skin by Frieben in 1902. An interesting historical note on the early observations has appeared (176). Ultraviolet and burn cancers (177) are similarly well-recognized. Osteosarcomas following x-irradiation have been further documented. In one report (178) there are 17 patients with bone sarcoma, 16 of whom received their previous radiation for a benign condition. Million volt x-rays also induced a bone sarcoma after a latent period of only four years (179). Cancer of various sites follows the alpha particle radiation from the products of thorium introduced into man as Thorotrast. Hemangioendothelioma of the liver as recorded in the initial observation has been found by others (180, 181, 182).

Leukemia is said to have increased in incidence (183) two and one-half

times between 1920 and 1950. The natural history of the disease is also changing as shown by increase in the mean age at the onset of acute leukemia in adults (184). Some feel that environmental factors, such as ionizing radiation, may be partly responsible (184, 185). Indeed, the evidence is daily becoming more compelling. The studies on increased incidence of leukemia in physicians in the United States have been continued (186) and fortify the earlier impression. Further reports on the atomic bomb survivors showed that the leukemogenic effect of a single explosion is quite high (187). Early reports (188, 189) of an increased incidence of leukemia and "aplastic anemia" after x-irradiation treatment of ankylosing spondylitis have been followed by a document which gives substantial support to this hypothesis. In a study (190) of 13,352 patients with spondylitis treated by radiation, 34 cases of leukemia and six with aplastic anemia were found, where the usual expectation in the sample was 2.9 and 0.3 cases. That the spondylitis alone was not responsible has been shown by Abbatt & Lea (191). In another study from England, Stewart *et al.* (175, 192) interviewed the mothers of children dying of leukemia, other malignancies, and other causes. They found that diagnostic x-ray of the abdomen during pregnancy was done twice as frequently in the mothers of the leukemic children. X-irradiation of the thymus in infancy has been followed by acute lymphocytic leukemia (193). Finally, the use of I^{131} in the treatment of thyroid cancer has, in two of 16 patients, been followed by proven myeloid leukemia (194).

Another tumor which is said to be on the increase is cancer of the thyroid (195). The original observation made by Duffy & Fitzgerald (196) that x-irradiation of the thymus in infancy was related to the induction of cancer of the thyroid has been supported by others. Simpson & Hempelmann (197) report a follow-up of their study of 1722 children given x-irradiation to the thymus. Ten of these developed cancer of the thyroid as compared to none in the untreated siblings. Leukemia, thyroid adenoma, and osteochondroma of the shoulder were also significantly higher. Several investigators have studied intensively all the children with carcinoma of the thyroid seen in their clinics. Clark (198) found that of 15 such patients, all had received therapeutic radiation in early childhood. Majarakis *et al.* (199) report that 10 of 15 patients had received radiation, but in 10 patients whose onset was before the age of 10, all had been radiated. Others have noted a definite but less striking relationship (200, 201). One dissent has appeared (202) with data showing only four children developing cancer of the thyroid after 750 r delivered to the tonsils of 2500 patients. However, the author followed only 480 patients. If one assumes an equal prevalence in the patients not followed, the 21 instances thus calculated would represent a greater morbidity than in Simpson's study. Another problem concerns the vigor with which the history of previous radiation is sought. Fetterman (203) found that of 10 children with cancer of the thyroid, four had received previous radiation. When the parents of the others were questioned

at length, four others finally remembered radiation of lymph nodes of the neck or tonsils. The entire matter is summarized in an editorial of the *British Medical Journal* (204) and the conclusion is one with which most will agree—that therapeutic radiation with x-ray should not be given to children for benign conditions; I^{131} for either diagnostic or therapeutic purposes should similarly be avoided in children. The responsibilities of the medical profession in the use of x-rays are clearly spelled out (205).

Viruses as etiologic agents of cancer.—One of the outstanding discussions at the Third National Cancer Conference was that of Stanley (206) in which he stated "The experimental evidence now available is consistent with the idea that viruses are the etiologic agents of most, if not all, cancer, including cancer in man." As many recognize, the advances in virological concept and technique of the past few years require the reexamination of the possible virus causation of all diseases of unknown etiology, including cancer. Some of these problems are discussed by Burnet (207). The new techniques have been applied to some of the classical virus-induced experimental tumors. Bryan *et al.* (208) in a study of the Rous sarcoma, and Beard (209) in studies on the avian leukoses, emphasize dose-response relationships in the problem of virus masking. Bryan found that the amount of extractable virus is related to the initiating dose, and showed that the absence of demonstrable virus does not mean that the tumor is of nonviral origin. Beard emphasized that most instances of so-called masking have been a matter of low concentration of virus particles. Gross (210) made the initial observation which started the present emphasis on the study of the induction of mouse leukemia by cell-free extracts of animal tumors. In his latest publication (211), he found that different tumors contained different concentrations of agent, and by proper selection a highly potent strain was developed. Stewart (212) and Woolley & Small (213) have confirmed Gross' initial observation. The cell-free agent from mouse leukemia has induced both leukemia and parotid tumors in the recipients. Stewart *et al.* (214) have used monkey kidney tissue culture and chick embryos for incubation of the cell-free agent obtained by extraction of the induced parotid tumors. Newborn mice inoculated with the cell-free fluid from the tissue cultures developed tumors of parotid, submaxillary, and sublingual glands, thymic tissues, adrenal medulla, and breast. The tumor extracts incubated in this fashion by classical virus methods, have produced an agent or agents capable of inducing a variety of neoplasms. Ehrlich ascites tumor has been found to induce leukemia in both newborn (215, 216) and adult mice (217). Fowl leukosis virus (218) induced renal adenomas when introduced into young birds.

All of the work cited has been done in animals which the reviewer has promised to neglect. It is referred to because it provides some of the background for Stanley's statement about the possible virus etiology of cancer in man. Viruses obtained from human tumors have, in the past, produced diseases in animals. Generally, this disease in the mouse has not been

neoplastic in nature. One such report on Hodgkin's disease has appeared recently (219). This material produced encephalitis but no tumors in mice. There is no reason a priori why a tumor-inducing agent in man should not produce disease other than tumors in the animal, but generally this circumstance has been interpreted as being due to a latent virus, not of etiological significance, in the tumor of the patient or in the tissues of the recipient animal. A different situation is described by Schwartz *et al.* (220). They were able to induce leukemia in AKr mice by inoculation of cell-free filtrates of the brains of patients dying from leukemia. AKr is a high leukemia strain, but the authors believe their results to be of significance because the inoculated mice developed leukemia long before any of the controls. This first step into the problem of virus etiology of human cancer requires further elucidation, but is no doubt the fore-runner of others, and perhaps by the time this review appears the virus etiology of at least one cancer in man may be established.

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DISEASES OF THE NERVOUS SYSTEM[1]

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Several areas of interest in diseases of the nervous system have commanded more attention than others recently. To single out a particular area as being more prominent than another would be difficult. There can be no question, however, of the major unanswered question in neurology, namely, that of the hoped-for effectiveness of the Salk vaccine against poliomyelitis, one of the most dreaded and disabling diseases of the nervous system and one for which so little has been offered in the past in the way of protection by immunization. The neurologist, the profession at large as well as the general population, eagerly await the slowly accumulating statistical reports from which the answer may not be forthcoming for several years.

Beyond this curiosity has been a concerted effort focussed upon the rapidly developing field of neurochemistry and neuropharmacology of the nervous system as it applies to both nervous system diseases and mental disorders. The momentum of effort in this has grown tremendously during the past year and has provided a terrific stimulus to and impact upon the field of psychiatry and for that reason has attracted a great deal of attention. Heretofore, the approach to problems in the psychiatric field has been limited chiefly to psychological dynamics until, by chance, it was discovered that alteration of neural metabolic functions, artificially induced, resulted in improvement of conditions which psychiatrists felt were not accessible from a therapeutic standpoint.

The trend in neurology and psychiatry presently is toward the biochemical concept of disease processes. This has come about as the result of outstanding work in the basic science of both fields, in neuroanatomy and neurophysiology, and in electrophysiological studies. There is also the added impetus given to this trend by the now rapidly moving and developing field of neurochemistry and experimental neuropathology which has arisen out of basic biochemical, metabolic, and neuropharmacological research. What was referred to about 25 years ago as "biochemical lesions" is now becoming a reality, and fosters the hope of rescuing medicine from an empirical status with respect to many disorders, particularly of the nervous system. Advances in techniques, the development of the electron and ultra-microscope, tissue culture and analysis, the assistance afforded by isotopic studies, and *in vitro* and *in vivo* studies of neural tissue activities have opened up an entirely new approach to the study and understanding of pathological changes in nerve cells and neural tissue. Matters of

[1] The survey of the literature pertaining to this review was concluded in September, 1957.

inhibiting or enhancing cellular processes and improvement of metabolic function have aroused interest in concepts which concern not only the maintenance of the state of aliveness of nervous system tissue, but also its correlation with alterations of metabolic or biochemical function and, perhaps, behavior.

All of this has set into motion concerted investigation in the field of neurology never approached before. The wider recognition of the importance of intracellular enzyme and other metabolite systems, ion functions, and specific inhibiting or enhancing effects has resulted in increased understanding of many of the "mystery disease" problems involving neurology. The past few years have been distinguished by a stepped-up pace in relating biochemical changes to tissue or tissue function changes. This period holds a great deal of hope for conditions in which help had previously been limited or nonexistent. However, concrete results from this concerted effort are not yet available.

Nevertheless, much has been accomplished toward a better understanding of many disorders, notably the studies relating to cerebral circulation and vascular disorders of the brain, the added diagnostic techniques and laboratory aids in recognizing nervous system disorders, plus the introduction of biochemical approach to the etiology and attempts at therapy in the degenerative disorders, many of which have related genetic factors. Increased life expectancy has increased the need for understanding and meeting problems concerning aging and rehabilitation, or indeed the problems of the physically handicapped regardless of age.

Infections.—Infections of the nervous system have become less prominent because of the improved general control of infection by antibiotics. This may not be necessarily true for viral infections of the nervous system unless it be in connection with poliomyelitis. Many unanswered questions still exist in evaluating the effectiveness of the Salk vaccine. The period of uncertainty in regard to the safety of its use seems to have passed. Its more extensive availability and distribution to age categories beyond childhood should bring forth data leading to reliable information although, at this time, insufficient data do not permit critical or statistical evaluation on a large scale. Isolated reports (1) seem to indicate that the long-sought assistance by vaccination against poliomyelitis is a significant advance.

There is still a prevailing opinion that bulbar poliomyelitis has a correlation with preceding tonsillectomy or surgical procedures of the oral and upper nasopharynx regions.

The interest aroused by the Salk vaccine administration has also resulted in a greater appreciation of multiple occurrences of poliomyelitis in a family. Similarly, second attacks of poliomyelitis have been noted, the implication being that immunity for one strain of poliomyelitis does not provide such immunity against other strains of the virus. Even though there has been decreased interest in the value of gamma globulin in reducing the incidence of poliomyelitis, it is still used despite its doubtful value for contacts of poliomyelitis. In this respect it is generally accepted

as having no value in the treatment of measles encephalitis (2). More encouraging is the reported beneficial effect of corticotropin in measles encephalitis (3).

Encouraging reports continue to appear of the treatment of herpes with cortisone or corticotropin, and indicate that topical application of 1 per cent hydrocortone ointment twice daily also effectively relieves pain and speeds healing of the skin lesions of herpes in most patients (4).

Tuberculous meningitis.—Survival from this disease presently continues to average somewhere between 50 per cent to 80 per cent in different series since therapy with streptomycin, *para*-aminosalicylic acid (PAS) and isoniazid (INH) have been introduced. Mooney (5) has observed an increasing incidence of ocular muscle complications where he suspected that papilledema was present and caused by tuberculous arachnoiditis or by interference by strangulation of pial vessels going to the optic nerves and chiasm. If the fundus deteriorated despite treatment with cortisone, Mooney advised neurosurgery for decompressing the optic nerve and removal of its arachnoidal adhesions.

Combined cortocosteroid or corticotropin therapy (6) is now advocated in addition to streptomycin, *para*-aminosalicylic acid, and isoniazid in order to prevent the formation of plastic, adhesive tuberculous exudate and thus avoid such complications as obstruction of foramina and development of hydrocephalus or cranial nerve palsy or other neurologic sequelae to heavy exudate formation. Caution must be exercised, however, in that the use of steroids should be limited to cases where there is no serious pulmonary tuberculosis. Steroids suppress inflammatory response, impede formation of granulative tissue formation and fibroblastic repair, and tend to offset the repair process in pulmonary tissue, whereas they are helpful in reducing exudate formation intracranially.

Aseptic meningitis.—This disease still offers a problem for clinical diagnosis. Frequently, antibiotics are given before the opportunity for isolating an infective agent is present, so that many cases of meningitis are never diagnosed as to type. It is frequently diagnosed as nonparalytic poliomyelitis but there are other viruses that may present a clinical picture similar to that of aseptic meningitis, notably Coxsackie B viruses as reported by McLeod and others (7). Lack of rapid laboratory tests or of facilities for virologic study are probably major difficulties in the diagnosis of aseptic meningitis. It is to be hoped that the increasing technical advances in virology will offset the present inability to establish specific diagnoses in cases of aseptic meningitis.

Among the drugs which may cross the blood-brain barrier and thus be useful in treating these cases are tetracycline and chloramphenicol (8, 9).

In general, infections of the nervous system have become less prominent, except for those owing to viruses, because of the effective control of other types by the antibiotics. Central nervous system complications in infections have been tremendously reduced, notably in those infections which formerly gained access to the meninges and cerebrum from in-

fected neighboring structures, such as the sinuses and mastoid cells. Brain abscess and dural sinus thrombosis are very uncommon occurrences now. The tendency toward early treatment of nasopharyngeal and middle ear infections with antibiotics has reduced the incidence of such complications to a very low figure. In this respect, similar management has also lowered the incidence of Sydenham's chorea considerably.

The prognostic value of the electroencephalogram in cases of meningitis and encephalitis is still commonly overlooked as a means of detecting early neurological sequelae, particularly seizure states in any type of encephalitis. The presence of focal or general electroencephalographic abnormalities found early in the course of an encephalitic infection, frequently ushered in by convulsions, call for serial electroencephalographic recordings at intervals of four to eight weeks to note recession or retention of focal or generalized seizure patterns. If seizures continue or appear immediately after the acute phase of encephalitis has passed, recordings should be made more frequently. Anticonvulsant therapy should be initiated early if persistent findings are obtained in the electroencephalogram studies.

Vascular disorders.—Of major interest to a long-neglected problem is the increased attention now being given to the dynamics of some types of vascular disorders of the brain. There are still gaps in accurate knowledge of cerebral circulation and vasculature. Improved techniques have made it possible to visualize and demonstrate dynamics of the cerebral circulation. This has been done by stereo-roentgenographic or serial angiographic studies of vessels in the living brain, or by studying the vasculature after death by injection of red lead powder or liquid red lead compound in a vinylite acetone medium in a technique introduced by Kaplan (10).

Experimental studies of great importance in respect to production of cerebral infarction by venous distention have revised concepts of infarction causation and also have given proof of the existence of the often doubted existence of vasospasm in cerebral vessels. Denny-Brown, Horenstein & Fang (11) have shown vividly the dynamics that result from cerebral venous distention in addition to the convulsive discharges by the neurons during ischemia and the rapidity of neuron death therein. They proposed an ischemic necrosis or "retrograde ischemia" for the cerebral tissue change that resulted. Of interest is the fact that this tissue change may not appear until ten days or more after production of increased venous distention. By introducing a polarographic method to demonstrate the readjustments in the level of oxygen availability in the area of lesion production, a correlation could be established with concurrent electroencephalographic change. Their findings indicate that the basic feature leading to lesion production is an intense spasm of smaller arterial vessels produced by a critical degree of sudden distention of the vein to the area. The eventual lesion developed as a fairly sharply demarcated one which was drained by the involved vein. It was difficult to determine the degree and extent of recovery of tissue function after production of critical hemodynamics. An encouraging observation was the important demonstration

of great variability in the extent of collateral circulation provoked by the procedure, proof that such circulation not only exists but may be the important factor in determining the degree of recovery.

In this work, Denny-Brown and his group attempted unsuccessfully to modify the effects by previous stellate ganglionectomy and sympathectomy, giving evidence thereby that local nervous vascular control mechanisms are most likely responsible for the small arterial vessel spasm and that this mechanism is independent of autonomic reflex action. The deduction was made that a sequence of a retrograde wave of distention occurred which then was passed on from vein to arteriole through the capillary network and that this provoked a reactionary contraction in the smooth muscle of the arterioles. This resembled the phenomenon observed in performing arteriograms by forceful blanching of head vessels and observing radiologically spasm of parts of the internal carotid system. Presumably, cerebral vascular accidents which lead to ischemic necrosis following arteriography were produced by a similar mechanism of retrograde ischemia, the critical factor being production of capillary stasis. The important observation made by this group was that if this stasis persisted for ten seconds or longer necrosis would develop. With an incomplete return of hemodynamics and oxygen availability to an involved area, a uniform pattern of necrosis would follow which could be detected by sludging of red corpuscles and seepage of plasma from the vasoparetic vessels into the surrounding cerebral tissue. Their histologic studies were also of interest in that they demonstrated the serial appearance of large mononuclear cells, plasma cells, and lymphocytes in the peri-adventitial space of the area of future retrograde ischemic necrosis. This would be followed by fat granule cells in the zone of capillary proliferation, a point of differentiation from the appearance of stasis and inflammatory necrosis production in cerebral tissue.

If the changes were studied over a period of time, polymorphonuclear response appeared by the second or third day with partial phagocytosis of the breakdown products of hemoglobin. This would then be followed by large numbers of macrophages in the periphery of the infarct by the third or fourth day. These were found to multiply on the outer surface of capillary loops and to develop rapidly into Gitter cells with progressive erosion of infarct with Giant cell formation in the more resistant areas.

Continued efforts have been made in the use of anticoagulants in cerebral thrombosis. Millikan and his co-workers (12) have been active in this effort, particularly in basilar artery thrombotic syndromes. In their hands, apparently, anticoagulant therapy has become more impressive. However, a division of opinion still exists as to the degree of risk involved, not only because of the difficulty in differentiating hemorrhage from thrombosis, but also because hemorrhage may occur from the area of infarction even if thrombosis exists as a result of too much lowering of blood coaguability.

Continued use of cortisone or related steroids in the immediate therapy of cerebral thrombosis or embolus-thrombosis formation, as well as five to ten min. inhalations of 5 per cent carbon dioxide and 95 per cent oxygen

at hourly intervals for the first 48 hr. after onset of symptoms, and then for an additional four or five days during daytime hours only, probably represents a compromise with the reluctant use of anticoagulant therapy. Existing evidence of its benefits is not striking from a statistical standpoint.

It is well recognized that angiography plays a great and important role in the visualization of vascular lesions and in differentiating them from other lesions. It has also been considered helpful in the recognition of suggestive symptoms produced by atheroma or thrombosis even though the procedure is not without risk, particularly when moderately advanced atherosclerosis or arteriosclerosis is already present. The incidence, however, of complications following angiography is declining.

Neurologists find themselves in the same state of uncertainty as do internists and cardiologists with respect to the role of cholesterol in atheroma development in blood vessels. Cholesterol-blocking agents, presumed to be effective in either the intestinal or liver absorption of cholesterol elements, have been introduced. Trial use of these agents is being carried on to determine their effectiveness in controlling or impeding embolus-thrombus formation in cerebral vessels of individuals who give prodromal indication of impending cerebral vascular accidents, or who have had minor, transient cerebral circulatory manifestations in the presence of elevated blood cholesterol levels. This has come about because of the trend in neuropathology toward attributing the majority of cerebral vascular disorders to atherosclerotic fragment dislodgment with subsequent embolus-thrombus formation or occlusion of atherosclerosis vessels. Studies are being conducted to estimate their protective value for individuals who give indication of threatened circulatory difficulty or for individuals who have had minor strokes or transient cerebral circulatory disturbance including the group which has had seizure manifestation. The postulate is gaining support in view of the work of the Boston group under Denny-Brown, although the general consensus is that the role played by the cholesterols in atheroma and thrombus production is debatable. There is some growing belief that the transaminase reaction may be of value in these situations. Preliminary and unreported trails of 2 cholesterol blocking agents in selected cases with elevated blood cholesterol and cerebral circulatory manifestations have been conducted by Klingman (13) for over two years [see also (13a)]. Total blood cholesterol levels have been maintained within the normal range or below, and there have been no further cerebral circulatory symptoms.

A newly reported technique considered to be noteworthy in the treatment of intracranial aneurysms is an innovation introduced by Dutton (14). It is particularly designed for treatment of aneurysms with a broad neck previously demonstrated by angiography but in which proximal ligation or trapping or exclusion of the aneurysmal sac directly by strictly neurosurgical methods is not possible. Dutton has invested the aneurysm and vessels with an unyielding support by the use of a dental syringe of acrylic methylmethacrylate into a firm encasement, polymerization from a semifluid state to a firm encasement being complete within twenty minutes. This has im-

proved the outlook greatly for preventing rupture where surgical procedure is difficult and where the aneurysm nevertheless is approachable by craniotomy.

Early recognition of internal carotid artery thrombosis, which may be followed by progressive cerebral infarction, can lead to successful extraction of the thrombus and is an impressive example of the important role assumed by angiography as a diagnostic aid in intracranial lesions, just as dural sinograms in infants are providing additional diagnostic aid to the surgeon and to the clinician. Improving techniques, development of less toxic contrast media such as diatrizoate sodium Hypaque sodium and renografin (15), and determination of the safest dilutions of preparations to be used, are reducing the risks attendant upon the use of arteriography in demonstrating anomalies, aneurysms, expanding lesions, subdural hematoma, and arteriovenous shunts. Improved methods of seriography arteriography have replaced to a large extent the need for air study, in particular permitting visualization of the venous aspects of the cerebral circulation, and especially detection of certain midline lesions which do not distort the large arterial channels. Displacement of the deep cerebral veins and of the vein of Galen is of extreme importance, especially of the anterior convexity point.

Visualization of the vertebral artery region has been much improved by development of the technique whereby a catheter is passed from the radial artery into the subclavian artery, thus including the vertebral in the radiographic study.

Attempts to correlate electroencephalographic findings in subdural hematoma before and after operation with information derived from cerebral angiography have led Chusid & de Guiterrez-Mahoney (16) to conclude that cerebral angiography is a more reliable and accurate test for the demonstration of hematoma formation, particularly supratentorial subdural hematoma with head injuries. In their study, fatal cases of dural hemorrhage resulted from transient occlusion of the posterior cerebral arteries secondary to incisural herniation, as well as compression of the upper brain stem and hemorrhage into the basilar and tegmental portions. Of interest was their observation that *contre coup* mechanisms may effect the electroencephalogram independently of a subdural hematoma. However, their over-all figures indicate a 70 per cent lateralization of major electroencephalographic abnormalities coinciding with the site of hematoma formation.

Cerebral trauma.—Where a complaint of vertigo, dizziness, or giddiness is part of the postconcussion syndrome, evaluation of this complaint as part of the clinical bedside examination has again been described as having significance by employing the technique of head posturing and noting the effects upon postural nystagmus. Savitzky (17) had noted this previously, and Klingman's discussion of his presentation of the significance of the head posturing in addition to the discomfiture on lateral gaze has been restated by Harrison (18). This is a valuable bedside observation and one which can also be applied in other than the postconcussion syndrome: vertigo, giddiness, wavering of objects, confusion in crowds, and particularly in

to-and-fro traffic where the effects of shifting gaze and head movements accentuate the complaint. Harrison's additional observation concerned the alteration of caloric tests in the form of either reduction of reaction to stimulation in one or the other ear or a preponderance of nystagmus occurring in a particular direction. In head posturing, nystagmus is induced by having the patient recline with the head down first on one side then on the other, and suddenly lowering the head over the edge of the bed. Nystagmus induced in a short burst spontaneously or by gazing laterally at the examiner's finger, is accentuated in the direction of the under ear with the head resting on one side. It may diminish if the patient does not have too much discomfiture.

If the patient assumes the upright or sitting position, nystagmus may again appear in a short burst spontaneously or in following the examiner's finger in the opposite direction. In both positions, the nystagmus tends to be diminished or abolished with immediate retesting. In cerebellar lesions these findings are not so pronounced. The observation is considered significant in detecting objective evidence of a post-traumatic state resulting from faulty postural neural mechanisms involving central connections to the cerebellum or from labyrinths, or it may be caused by damage incurred by the inner ear and its connections in the head injury. Harrison is inclined to favor the origin as arising from damage to the inner ear.

The associated discomfiture on lateral gaze and the finding of altered postural nystagmus are not accompaniments of the post-traumatic neurosis state; the complaint of discomfiture on lateral gaze is not common in the symptomatology of the neurotic. Findings of this nature may be the only objective evidence to explain vertiginous complaints in the post-traumatic state, and such testing should be a matter of routine in differential diagnosis and should provide assistance in establishing a diagnosis of a post-traumatic state.

Basal ganglia.—Interest is naturally high in any form of therapy in or clues to the etiology of the hyperkinesias as well as the Parkinsonian states, hepatolenticular degeneration, mixed involvement of basal ganglia and corticospinal systems as seen in the cerebral palsied or in chorea, either Sydenham's or Huntington's, where pure basal ganglia involvement is not a settled issue, or in other transitional forms of hereditary degenerative disturbances. For these disorders several avenues of approach are being investigated. One is the approach to fundamental metabolic derangement as exemplified by the studies on hepatolenticular degeneration in which copper and amino acid metabolism derangements have led investigators into a search for still undiscovered metabolite factors. Other disorders such as the symptomatic reflex, Parkinsonian states, and other hyperkinesias are being studied by Cooper's (19) neurosurgical procedure, i.e., injecting absolute alcohol through stereotaxic aid into the mesial portion of the globus pallidus. This procedure is also being tried in cases of cerebral palsy with mixed signs and symptoms of corticospinal and striatal nature. Relative safety for the procedure is claimed for the young as well as the elderly patient. The test of time will most likely provide the answer as the history

of previous attempts at interrupting the involved pathways in basal ganglia disorders has been disappointing. Even though immediate suppression of abnormal involuntary movements has been achieved by such interruption, the slow, gradual reappearance of the former state or a variable of it eventually result. This might be expected in all but static lesions in that many of the conditions are due to slowly progressing degenerative changes.

In some of the basal ganglia disorders, several of the rapidly growing group of tranquilizing agents are helpful in giving symptomatic relief. Despite the fact that chlorpromazine hydrochloride may produce Parkinson-like alteration of muscle tonus, it may be beneficial in low dosage in reducing the abnormal movements associated with striatal system disease. Combining the most individually effective tranquilizer with the atropine-like spasmolytics used in the Parkinson state may supply assistance by mood elevation, reduction of anxiety and the selfconsciousness component so often present. Combining the spasmolytics with tranquilizer and mood elevators, of which there is a choice of many, e.g., dextro amphetamine sulfate (Dexadrine Sulfate) and other amphetamine derivatives as such or in the sustained action form, sometimes makes the difference between near success and failure in controlling the Parkinsonian and variable personality reactions. Postulating an added value of the alerting agents as, for example, the amphetamine group or piperidyl hydrochloride (Meratran Hydrochloride), has been the questioned effectiveness of stimulating a still debatable suppressor corticospinal suppressor mechanism. This value is quite apart from the benefit to be gained from their alerting properites in overcoming drowsiness and sense of fatigability. Klingman has combined the effects of the tranquilizers with the amphetamine-like preparations in treatment of the so-called "motor neurosis" syndrome including torticollis, torsion, and mobile spasms with eventual disappearance of these therapeutically resistant conditions. His assumption is that the majority of these are psychogenic in origin and that these agents are beneficial in establishing new conditioned reflex mechanisms involving disturbances of motor function, while at the same time permitting psychotherapeutic measures to be more acceptable. The program also has avoided the notorious appearance of marked depressive or other severe psychotic reactions when the patient is deprived of the abnormal involuntary movement. An added tool seems to be provided for the psychotherapeutic management of such individuals following relief of their psychogenically originating movements. Fourteen of sixteen of Klingman's (20) group were no longer on medication after varying periods of time, the intervals ranging from four to six weeks to four to six months. In the same hands, essential or familial tremor has shown equally good response particularly in the patient's associated anxiety concerning outcome, or the element of self-consciousness produced by the act of signing documents in public, using tableware in public, etc., and accentuated under conditions of stress and excitement. Use of any of the agents must be individualized as there are great variabilities in response.

These agents are also useful in the management of rehabilitation in

neurological conditions which include such conditions as stuttering and stammering, cerebral palsy, Parkinsonism, hemiparesis and hemiplegia and, with vacillation of the condition, in multiple sclerosis. Possibly influence upon mood, production of a venturesome attitude, establishing a better sense of security, overcoming defeatism and self-conscious factors, aside from the effects upon the underlying condition, may all be factors in any improved state of function and performance.

Epilepsy.—Much investigative effort continues in the field of neurophysiology, neuroelectrophysiology, neuropharmacology, and neurosurgery in regard to epilepsy. At this time the conventional idiopathic epilepsy of former days is gradually being divided into symptomatic and centrencephalic attack disorders. More and more consideration is being given to the fact that the seizure states are one disorder in which a trigger mechanisms locus or focal region exists which gives expression to the seizure picture. The seizure picture depends upon each individual's neuronal readiness to direct the type of seizure, based ultimately upon neurochemical change related to the neurone discharge phenomena and their method of spread.

The ability to recognize and localize psychomotor epilepsy and relate it to the anterior or midportion of the temporal lobe is of major importance, not only because of the variety of clinical manifestations which psychomotor epilepsy may assume, but because activating techniques may be necessary to demonstrate the electroencephalographic evidence of presence of a temporal lobe focus. Inasmuch as psychomotor seizures are much like *petit mal* in their resistance to therapy, and in view of the fact that many psychomotor seizures are caused by localized tissue changes of the anterior portion of the temporal lobe, they deserve consideration for neurosurgical removal of the lesion when medical therapy falls short of success or control. Hopes are higher for control by medication by addition of primidone (Mysoline) and celontin to the list of anticonvulsant drugs. Results, however, are gratifying for control of the psychomotor component by surgical removal of the anterior temporal lobe in psychomotor seizures but roughly 50 to 60 per cent may still be subject to *grand mal* or atypical *grand mal* seizures, although relieved of the psychic and automatism components of the psychomotor attack. Control of the *grand mal* component by anticonvulsant medication is much more successful following surgical removal of the lesion.

Tranquilizing drugs are likewise being added to the anticonvulsant medications as adjuncts in the treatment of seizure states (21). There is still doubt that true anticonvulsant properties are to be found in tranquilizers, but they have proven their usefulness in either reducing the emotional trigger mechanism-precipitating factor in seizure production, or in potentiating anticonvulsive seizure medication effect. For that reason, care must be exercised with respect to the production of drowsiness, a false sense of fatigability, or overrelaxation bordering upon drowsiness.

There are a number of agents undergoing trial in the seizure states which are not commercially available as yet. Some of these are presumed to influence factors involved in the biochemical or electrophysiological states

specific to the seizure manifestation. This encourages the hope that investigations in this direction are leading more directly to the causative factors in the epilepsies rather than merely offering a control method by reduction of excitation factors which are not necessarily features of the genesis of the neuronal "readison" based upon neurochemical alterations.

The availability of diphenylhydantion sodium (Dilantin Sodium) for intravenous use in actual or impending status epilepticus in dosages of 250 mg. to 500 mg. given at the rate of 100 mg. per min. has added another therapy of value in cases where it can also be given alone or in combination with sodium phenobarbital. A lower dosage of the latter is indicated in combined therapy intravenously is used for controlling status epilepticus.

From the standpoint of interest in the electroencephalogram, it seemed generally agreed upon at the 1956 meeting of the American League Against Epilepsy that its value is that of a laboratory diagnostic aid, and that one does not treat the electroencephalogram in seizure states but the patient. It may serve in some instances, but certainly not in all, as a guide in therapy, particularly in the program of gradual reduction of medication after seizure control has been obtained. Caution is still advised in too rapid a reduction of anticonvulsant agents in this period, the time intervals varying in different clinics from six months to several years. Routine serial electroencephalograms, together with complete neurological examination and serial skull x-rays, are insisted upon in well-conducted seizure clinics, particularly for the individual whose seizures appear in late adolescence in in the twenty to twenty-five year age group and beyond. The incidence of organic lesions and seizures on a symptomatic basis increases greatly beyond the childhood years. Reassurance by arteriogram or pneumoencephalogram is also recommended if these measures are indicated and justified.

Among the other attack disorders are the recurring headache group, whether tension or typically paroxysmal migraine in nature. Again, the generally free usage of tranquilizers has altered the picture for this group of disorders where strong emotional and personality factors play such a prominent role. Although no large scale studies are reported, one cannot help but gain the impression from practitioners at large that practically all of the tranquilizers are being used freely and that they are helpful. Friedman & Klingman (22) have reported their experience in the use of the Rauwolfia preparations. Although both report effectiveness for this particular group, Klingman's experience with Rauwolfia in the true migraine group as well as in atypical facial neuralgia is more favorable. Both have noted improvement in the cases with accompanying essential hypertension, but Klingman is of the opinion that it also serves to influence or regulate the specific vascular mechanisms which result in the eventual headache expression. Recognition is also given to the fact that the Rauwolfia preparations have a tranquilizing effect and that, furthermore, patients learn to adjust to the factors which have previously caused their personality distress. This adjustment also makes them more amenable to appropriate psychotherapy. Observations made by Klingman indicate that the patient with true migraine,

once on a regular intake of Rauwolfia preparations, will frequently respond to the conventional abortives such as Cafergot or Fiorinal, or combinations of barbiturates, caffeine, and analgesic, during the period of an aura, especially in ophthalmic migraine. Prior to the use of Rauwolfia preparations there was poor response to such abortives. Although Klingman did not use the double blind method in his series, all cases were furnished their medications which were replaced at intervals by placebos of the same color, size, shape, and taste, only to have their migraine episodes recur following the substitution. In some of these cases no attempt was made at psychotherapy, whereas, in others it was. In atypical facial neuralgia definite benefit was similarly achieved when all other methods had failed.

Headache or cephalalgia arising from neck structures in connection with subluxation of cervical articulations in so-called "whiplash" injury has been attributed to compression of the vertebral artery and its sympathetic nerve supply (23). Even though the subluxation may be a transient one, there presumably is a dislocation of an upper articular process and compression of the vertebral artery and its sympathetic nerve against the margin of the foramen of the next higher transverse process. Koca's study of the mechanics of development of such factors included cadaver studies.

Spinal column and spinal cord.—In reference to the above effects of subluxation, the spinal column is receiving a growing attention relative to cord involvement secondary to cervical spondylosis (24). Pointed out several years ago it, nevertheless, is becoming more universally recognized in the differential diagnosis of such conditions as amyotrophic lateral sclerosis with onset in the upper extremities, progressive muscular atrophy, and dorsolateral sclerosis where there is no associated primary anemia or achlorhydria.

In reference to the upper cervical vertebrae it has been pointed out that in posterior fossa tumors in children under the age of eleven, with the exception of cerebellopontine angle tumors, when the index obtained from the ratio between the atlas-inion and the basis cranii is above 0.41 this should make one suspicious of a posterior fossa expanding lesion.

Myasthenia gravis.—Very much like progressive muscular dystrophy and the heredo-degenerative disorders of the nervous system, this condition is passing through a period of more intensive study on the part of investigators particularly with reference to biochemical factors of importance. At present there is a trend to use mytelase (ambenonium chloride) more freely, particularly if symptomatic control or benefit is not derived from neostigmine bromide (25). Mytelase and mestinon (pyridostigmine bromide) may have an advantage over neostigmine in some cases. In some, carefully adjusted combinations of these with neostigmine seem to be more effective than either preparation used alone. Variation in patient response is great, and use of any of these preparations must be highly individualized as to dosage and time intervals of administration.

Neuropathy.—It was pointed out by Sullivan *et al.* (26) that in polyneuropathy of unknown etiology, into which group most polyneuropathies

fall, one should not overlook the participation of the peripheral nervous system in amyloidosis. No particular feature of the neuropathy distinguishes it from other types. However, coexistence of concomitant alterations of mesenchymal tissue by amyloid changes establishes the diagnosis. The heart and larynx are most commonly involved, the vocal cords usually having a yellowish appearance, and a history of intermittent hoarseness or huskiness of voice is present. Reliance cannot be placed on the Congo red test, and the most helpful procedure is that of studying repeated biopsy specimens if the laryngeal examination is negative. Likewise, neuropathy may be associated with a history of migratory arthralgia, fever, malaise, weakness, occasionally leucopenia, elevated sedimentation rates, false positive serology, L. E. cells in sternal marrow study, and positive L. E. clot tests. Some or all of the above findings are present, and the nervous system involvement may also vary from a neuropathy form to one showing central nervous system involvement, often of permanent nature.

Concerted effort is being expended in "neurology concerned with behavior," in which the basic workers in neurology, the neurologist, the experimental pathologist, the neuropharmacologist, and the psychiatrist are approaching the matter jointly in probing for cerebral areas and neuronal mechanisms which influence behavior. This subject is a large one and can only be referred to briefly as indicating a trend in neurology and psychiatry toward future possible therapy in nervous system disorders as well as psychiatric disturbances.

Similar energetic investigations are under way in the degenerative disorders of the nervous system, many of which are related to genetic factors. These, as well as the metabolic defects, are being critically evaluated particularly through basic biochemical, neurochemical, and tissue assay methods as they apply to the afflicted individuals as well as to members of the family or to its antecedents.

Improved laboratory techniques and the development of diagnostic aids such as provided by chromatography, cerebral angiography, seriographic angiography, myelography and more elaborate and careful evaluation of leads to possible metabolite disturbances in the body fluids, tissue culture studies, neural as well as muscular, offer hope of uncovering causes and factors involved in many of the mysterious diseases of the nervous system.

In conclusion, one must recognize the growing interest in the physically disabled, many of whom suffer from neurological disorders. There has been an impressive increase in physician, family, community, and employer interest in establishing the philosophy that the physically disabled child or adult deserves equal opportunity with the normal for friendship and acceptance. Behavior and attitude toward the disabled individual should be based on knowledge and understanding rather than on emotionalism provided the afflicted has no associated mental disturbance. Furthermore, acceptance in a group situation or job placement, and inclusion in rehabilitation programs should be considered just as any other differences which exist among individuals. Fortunately, more and more opportunities are be-

ing provided by federal, state, and private organizations to meet not only the needs of the physically handicapped, but also the increasing needs of a population in which the aging and longevity factors have presented a changing picture. Neurology has been drawn into the changing picture as a member of the team in meeting the problems. These problems already confront not only the civilian practitioner, but even more dramatically, the Veterans Administration, which has an aging population of veterans for whom to care. The growing needs of future years are being anticipated by pilot projects already established by the Veterans Administration, and presently conducted by them.

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PSYCHIATRY[1]

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Introduction

The pace and variety of advances in psychiatry are increasing rapidly and, as Wolf (1) pointed out a year ago, techniques are developing which link it more closely to other areas of human biologic research. This does not mean that it should be restricted to the application of basic scientific methods alone. It must use these but it is imperative that it develop others, some so far unknown, in order to solve those complex issues which demand understanding in biologic, psychologic, sociologic, and philosophic terms.

Centenaries

The year 1956 marked the centenary of the birth of two great contributors to the development of psychiatry, Kraepelin and Freud. The former not only spelled out clearly for the first time the concepts of manic-depressive psychosis and dementia praecox but also established laboratories of psychology, pathology, serology, and chemistry in his clinic. His influence was basic, far-reaching, and greatly conceived within the tradition of the times. He proposed to pattern psychiatry along the lines of internal medicine, a conceptualization which was, of course, inadequate then and for decades to come. He did, however, supplant chaos in diagnosis with order (2). As Braceland (3) has said,

"the foundations carefully, methodically and devotedly laid by Kraepelin support the superstructure of the unified and comprehensive psychiatry we are trying to build. Psychiatric work of such cogency and scientific precision was never seen before Kraepelin: It remains as his monument and, in like manner, it is a monument to the profession which he adorned."

Freud's contributions are considered by many still more basic and more far-reaching, if turbulent. His anniversary has been accorded great acclaim. Jones, in a centenary lecture (4) and in the second volume of his able biography, helps us view the man, his influence and his frailties, clouded a little perhaps by the intimacy of his own participation in psychoanalytic developments (5). A series of essays published by the New York Academy of Medicine (6) helps explain the revolutionary impact of his work on psychiatry, related disciplines, and on contemporary culture. The castigation of Freud's views and works, so common in former times, still con-

[1] The survey of the literature pertaining to this review was concluded in July, 1957.

tinues and reached an erudite pitch in Bailey's Academic Lecture (7) on "The Great Psychiatric Revolution" before the American Psychiatric Association. Here, this eminent scientist criticized not only psychoanalysis but a number of other endeavours in psychiatry as well with a vigour which, had it been tempered with charity, might have been a real contribution to an enlightened evaluation. Admittedly, techniques whereby the validity of many psychological concepts may be judged remain to be elaborated, yet invective is no substitute for this shortcoming which is not so serious that critical appraisal is out of the question. Further evidence that some of Bailey's criticisms are in the process of being remedied by technical developments and the evolution of attitudes may be seen in the increasing frequency of meetings at which basic scientists and psychiatrists are exchanging facts and opinions to the mutual benefit of both parties. This process can be exemplified by the published record of a conference at which workers from disciplines as disparate as neurophysiology, sociology, and psychoanalysis met with the object of studying animal mechanisms from the cell to society (8). While such a meeting would have been an improbable and unfruitful effort ten years ago, it was achieved in 1956 with signal success with the examination of a hierarchy of scientific methods applicable to psychiatric research. The workers in the basic and the behavioral sciences were able to regard each other's findings and concepts without dismay, and indeed with the recognition of a common theme. This salutary meeting of minds with diverse approaches was appropriately summarized in a brilliant and witty fashion by a philosopher, who stressed the need for "tolerance of ambiguity" in creative science. This essay should be required reading for those trying to force psychiatric endeavours into the 19th century mould of mechanistic proprieties, and for those who delight in the wisdom of suspended judgment.

The year 1957 ushered in the centenary of two other distinguished contributors to psychiatric development. One, Wagner-Jauregg was, like Freud, a Viennese. He is known to nonpsychiatric circles for his Nobel Prize-winning development of fever therapy for general paresis. This particular achievement was only a high-light in a life devoted to an organized effort to understand man in organic terms. His accomplishments and character have been graciously described by Silbermann (9).

The Swiss psychiatrist, Bleuler, born the same year, achieved his greatness by an exercise of diligence and intellectual power of magnificent proportions. While his writings were epochal they did not lend themselves to concise formulation amendable to lay apprehension, nor to caricature, like Freud's. Even his great contribution on the schizophrenias was not translated into English for thirty years. It was most fitting that his anniversary was commemorated this year at the 113th annual meeting of the American Psychiatric Association by the Fellowship lecture of Zilboorg (10) who

discussed him in relationship to two of his great contemporaries, Kraepelin and Freud.

PSYCHOPATHOLOGY

The areas chosen for review under the somewhat inadequate rubric of psychopathology have in common the recommendations that they contain observations subject to validation and that they contribute not only new data but also important implications for psychiatric and psychologic theory.

Gastric function, orality, and depression—Investigations of gastric function have afforded a singularly fertile bridge between psyche and soma. Wolf & Wolff (11) made the first systematic effort to relate emotions and gastric function in a man with a gastric fistula, and Margolin (12) related unconscious mental processes emerging from psychoanalytic observations to gastric activity as recorded physiologically in a woman with a similar lesion. These investigations have been extended and amplified by the brilliantly executed studies of Engel, Reichsman & Segal (13) on an infant whose congenital atresia of the oesophagus enforced the establishment of a gastric fistula on the fourth day of life. The published details of this investigation concern gastric secretory, psychological, and behavioral observation in 59 experimental periods on the subject between the ages of 15 and 20 months. They identified six affects—contentment and joy falling under the heading of pleasure, and four kinds of unpleasure, namely depression, depression-unpleasure, irritation, and rage. The total hydrochloric acid secretion rate increased with outgoing affective states, whether pleasant or unpleasant, in contrast to the decrease which occurred with the depression-withdrawal reaction, as shown by a sad expression, inactivity, and flaccidity, progressing to withdrawal into sleep. Histamine given during the latter state had little effect on gastric secretion but led to a potent stimulation of hydrochloric acid secretion when the child showed outgoing behavior. They felt that these observations supported the psychoanalytic concept of an oral stage of development in which the establishment of relationships to objects involves a taking-in attitude. As this infant related in an outgoing fashion to the experimenter, her gastric glands secreted as if the emotionally charged (cathected) object was about to be ingested. The observational and theoretical importance of this contribution and a companion article (14), which deals more particularly with the depressive component in the infant, is beyond a cavil of doubt. In the latter paper, Engel & Reichsman (14) deal with the implications of their observations for an understanding of the problem of depression vis-a-vis earlier concepts of Abraham, Freud & Rado and the more recent formulations of Spitz, Bibring, Benedek & Jacobson. They postulate, on the basis of clearly presented data, that the depression-withdrawal phenomenon represents an inactive preoral, preobject phase in which physiological inactivity accompanies the behavioral withdrawal from contact with objects. This reaction

they found could be experimentally evoked by the introduction of a stranger into the child's cubicle. It could be dispelled by replacement with the familiar and fond figure of one of the investigators. It differed from the depression as conceived in classic theory which is seen as an active and restitutive endeavour to re-establish lost objects by oral mechanisms.

Perception and dreams.—The study of dreams and perception has received a staunch stimulus from the original and fruitful studies of Fisher (15, 16). In the earlier work he repeated, confirmed, and extended Poetzl's classical experiments on dream formation in which a picture was exposed to the subject for 1/100 sec. (tachistoscopic presentation) and the subject asked to record any dreams occurring on the night following. It was found that in the dreams the subject often reported details of the picture that had not been consciously recalled after the experiment—that is to say, there had been what Fisher calls preconscious perception. In the dreams these percepts retained the meaning of the object at times only, in other instances being treated as a concrete object without its meaning. The roles of suggestion, transference, dream distortion, and the relation of perception to unconscious wishes and drives are discussed. It was felt that preconscious perception might be termed "primary process" perception, implying regulation by the pleasure principle as opposed to "secondary process" perception (ordered thinking) controlled by the reality principle. In the second paper, Fisher describes the repetition and elaboration on the experiments of Allers and Teler in which a word association test was performed using as stimulus words the names of objects in tachistoscopically-exposed pictures presented minutes to days previously. In addition, subjects reported and made drawings of images developing after the stimulus and before the response word. Following this the picture was re-exposed at increasing intervals until all parts were clearly recognized and opportunity given to compare drawings to the original pictures. It was found, in confirmation of the earlier work, that preconsciously perceived parts of the briefly exposed pictures later appeared as conscious images. The findings also showed that the preconscious percepts of memory images were subject to transformations and distortions as shown in the previously reported dream studies and that emergence of these percepts into consciousness might be delayed at least as long as three days. This work contributes to an understanding of the chronology of dream formation and of the process of distortion which the author argues cogently as beginning at or close to the time of the imprinting of the preconscious percept in association with the day-residue experience. The implications of the study for various aspects of psychological theory and, in particular, that of perception are discussed.

Psychogenic orientation in gonadal agenesis and hermaphroditism.—The syndrome of ovarian agenesis, named after Turner and redefined by Albright *et al.* in 1942 (17), has been re-examined recently by Hampson,

Hampson & Money (18). The pathognomonic significance of these studies for psychiatric theory has been uniquely increased by the discovery that many of the cases had male chromosomes—in 11 of 13 in whom the pattern was determined in this series of 19 cases, the condition thus being better described as gonadal agenesis. In this paper, which concerns particularly the 11 chromosomally-male individuals determined by the skin biopsy test of Barr (19), all met the cultural and psychological standards of femininity. This implies that the individual's conviction as to sexual role is independent of cellular determinants. It was also concluded that the appearance of physical maturity is essential for the development of psychological attitudes appropriate to adolescence. Management called for honest discussion of the medical facts of the situation.

In a subsequent study of developmental sexual abnormality, Money, Hampson & Hampson (20) have described an investigation of hermaphroditism in 65 ambiguously sexed people, and demonstrated the unwisdom of assigning such cases to one sex or the other on the basis of a single criterion. As in the cases of gonadal agenesis, the chromosomal criterion should carry little weight. They described seven variables in hermaphroditism that may vary independently, namely, chromosomal, gonadal and hormonal sex, external genital morphology, accessory internal genital morphology, assigned sex and rearing, and finally, and most important, gender role with psychosexual orientation derived from experience. On the basis of the first three criteria seven categories of hermaphroditism have been described, but decision about the assignment of sex must be made on the basis of how well the external genitals lend themselves to surgical reconstruction to the assigned sex, or, in older patients the assigned sex and gender role must be supported because, with rare exceptions, hazardous psychiatric sequelae may follow. The psychologic management of parents and patients and the imperative need for clarity of explanation and frank discussion is emphasized. In a third article (21) these authors examine some basic sexual concepts arising from the above studies. They found that gender role and orientation were congruous with the assigned sex and rearing in 72 of the 76 cases despite contradiction with other criteria. The gender imprinting they believe began by the first birthday and a critical period was reached at 18 months. At two and a half years it was well established. The implications of these findings for instinct theory were considered. A fourth report of these investigators (22) to be referred to here concerns a psychiatric and psychologic appraisal of 94 hermaphroditic patients. On a four point rating scale, 63 were described as healthy, 16 mildly, 14 moderately and one severely nonhealthy. A relative lack of psychosis was most noteworthy. The unhealthy ratings were more common among the teenagers and adults and those in whom body morphology was ambiguous. Adjustment to therapeutically induced normalcy in adulthood

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proved to be psychologically difficult, especially in hyperadrenocortical female pseudohermaphrodites feminized by cortisone. In a still more recent report (23) which reviews their earlier work, these authors have succinctly summarized their views. They underscore one point of considerable significance, namely, the early imprinting of gender role and orientation which they believe may become so ineradicable as to seem an innate instinct. This they compare to the observations of the ethologist, Lorenz. The full implication of this remarkable work remains to be fully utilized by and integrated into the main stream of psychiatric thought.

Psychoendocrinology

A few years ago there was hope that endocrine studies might throw considerable light on psychiatric problems. This was particularly true of the interest aroused by the "cortisone" psychoses, but as the explanation for this exciting phenomenon was not forthcoming it became apparent that the solution was much more complicated than first thought, as pointed out by Cleghorn in the recent symposium on *Hormones, Brain Function and Behavior* (24). The allied topic of the organism's response to stress has also received closer scrutiny by clinical and laboratory investigators (25, 26) as befits an erstwhile satisfying but loosely elucidated notion. One intriguing area of active research is that of epinephrine and its chemical relatives. This rapidly developing field appears to be of signal importance in brain metabolism, merging as it does with studies on psychopharmacology.

Neurosecretion.—The concept of the brain as an organ of internal secretion has been referred to previously in this review (1). An instance of this still novel idea is the well-supported belief that hypothalamic centres secrete the neurohypophysial hormones oxytocin and vasopressin, incidentally the first peptidic hormones to be synthesized (27). The evidence for the origin of these substances in hypothalamic neurons and their transport down the axoplasm to the neurohypophysis has been reviewed by the Scharrers (28). The recently published symposium on *"Hypothalamic-Hypophysial Interrelationships"* (29) covers topics ranging from most of the important neuroanatomical details of the neuroendocrine complex to assessment of hypothalamic-hypophysial dysfunction in man. It also includes an account by Guillemin of his stimulating studies on the control of the release of ACTH by rat anterior pituitary tissue kept under tissue culture conditions. Such tissue ceased releasing ACTH soon after culturing, but the secretion of ACTH was initiated by including hypothalamic tissue in the culture, thus providing evidence for the existence of a hypothalamic stimulant of ACTH secretion. The existence of an ACTH-releasing factor (corticotrophin-releasing factor, CRF) in both the hypothalamus and the neurohypophysis was suggested by the work of Saffran & Schally (30) who, instead of using tissue cultures of rat anterior pituitary glands, merely

tested the ability of hypothalamic and neurohypophysial tissue and extracts to stimulate the release of ACTH from halved rat anterior pituitary glands in an acute (1 hr.) incubation. These authors observed that hypothalamic and neurohypophysial tissue stimulated ACTH release only when epinephrine or arterenol were added (30). Like Guillemin & Hearn (31), they found that commercial preparations of vasopressin (Pitressin) contained CRF, and while Guillemin failed to stimulate ACTH release with highly purified beef vasopressin, Saffran, Schally & Benfey (32) noted that the vasopressin lost ACTH-releasing activity on purification. The activity appeared in one of the impurities separated from vasopressin. Subsequently, Guillemin *et al.* (33) found CRF activity in hypothalamic extracts. The amino acid composition of CRF has been ascertained and described recently (34). Thus, another neural hormone, CRF, may be added to the list of endocrine products of the brain.

One of the features of the endocrine system is the presence of a negative feedback control in the case of most of the individual hormones. As the brain assumes a greater role as an endocrine organ, so the study of the effects of the various hormones upon brain function becomes of greater theoretical importance. In 1956 a conference was held on neuroendocrinology, dealing partly with the influence of steroidal (gonadal and adrenocortical) and thyroid hormones on brain function (35). While many important details were disclosed, the dearth of guiding principles emerging from the investigations reveals that the study of neuroendocrinology is in its infancy. However, we may look forward to the day in the near future when the study of the function of the brain as an endocrine organ will be coupled with the study of the other functions of the brain, as an integrating organ, as the determinant of behavior and as an organ of thought.

Pyrocatecholamines.—These substances, previously but less specifically chemically termed the "catecholamines," have been one of the main reasons for the new upsurge of interest in the chemistry of human behavior. So long as our knowledge of these substances was limited to the occurrence of epinephrine outside the brain there was little cause to implicate it in mental mechanisms. With the discovery of the presence of this and arterenol in the central nervous system the connection of the sympathetic nervous system with mentation and emotions acquired much greater pertinence and more pervasive meaning. The phenomenonal increase in concern was occasioned by several factors: by the surprisingly different pharmacological activity of the closely related compounds, epinephrine, arterenol, and *N*-isopropylarterenol (Isuprel) by the development of new methods for the chemical determination of the first two in minute amounts in body fluids by methods of fluorescence measurement; and finally by the exigency of psychiatry to grasp new clues. Perhaps the most sustained endeavour to find meaning in the secretion of epinephrine and arterenol in relation to

emotion has been made by Funkenstein who has recently reviewed his 10 years of research (36). In his book *Mastery of Stress,* in association with King & Drolette (26), he develops themes which are beyond the scope of this review, but it must be mentioned that from his study of basic physiological reactions his ingenuity and perceptiveness led him to apply a variety of psychological tests and cultural approaches which bid fair to provide new points of view and profitable insights which cannot fail to excite admiration, thought, and controversy.

An extension of the above studies is to be found in the measurement of pyrocatecholamines in various clinical states by Elmadjian, Hope & Freeman (37), who studied men under various stress situations, normal subjects, and schizophrenics (38). They contend that their data support Funkenstein's hypothesis that the active, aggressive subject has an increased arterenol excretion with or without elevated epinephrine, whereas the tense subject with a passive emotional display ("anger-in" category of Funkenstein) has more or less the reverse pattern. The great variation in individuals' patterns makes it difficult to establish any hard-and-fast rule about this. The authors base their discussion on the evidence of the basic sciences that differential secretion of pyrocatecholamines originates in the differential stimulation of hypothalamic areas. Garb, Tiwari & Chapman (39), noting some unusual pharmacological properties of Isuprel and having available Lockett's report (40) that this substance occurs in the animal body and may therefore be secreted in man also, have erected hypotheses that psychotic symptoms arise from interaction of epinephrine, arterenol, and Isuprel. Thus, Isuprel or a similar substance may be involved in anxiety, arterenol possibly in aggression and hostility, and both of them in states of mixed anxiety and hostility. A difficulty with these theories is the impossibility of testing them directly with present methods, none of which permits quantitative measurement of the extremely low level of Isuprel postulated to be required to exert these complex actions.

The view that a deranged metabolism of epinephrine is basic in schizophrenia has stimulated the search for differences in this respect between normals and psychotic individuals. Leach & Heath (41) have found that epinephrine is oxidized *in vitro* more rapidly, on the average, in plasma derived from schizophrenics than that from normal subjects. The agent responsible for the oxidation is claimed to be ceruloplasmin, the blue copper-transporting protein, and the authors speculate that schizophrenia is associated with an elevated concentration of this substance. The product of the oxidation is considered to be adrenochrome, the agent which the Saskatchewan group at one time considered to be "M-substance," i.e., their hypothetical specific etiological agent in schizophrenia. In a confirmatory note, Hoffer & Kenyon (42) have reported results similar to those of the Tulane workers, but claim that product is adrenolutin which they now consider the

more likely "M-substance." These oxidations are probably similar, or even identical in nature, to the oxidation of *N,N*-dimethyl-*p*-phenylenediamine by an agent in plasma, probably ceruloplasmin, as reported by Akerfeldt (43), and later Abood *et al.* (44). This oxidation was also more rapid in schizophrenics than in normals.

As interesting as these data are, the various authors mentioned are quite clear in disclaiming any degree of specificity for the reaction. Elevated rates of oxidation of the dye mentioned are found in numerous other diseases. Of course, the association of schizophrenia with these suggests the operation of additional physiological factors in this psychosis. In regard to the oxidation of epinephrine it must be emphasized that there are other mechanisms for the formation of adrenochrome, and eventually adrenolutin, e.g., by oxidation with cytochrome-*c*. Indeed, the cytochrome-mediated oxidation may occur under physiological conditions, something which is still to be questioned about the ceruloplasmin oxidation.

Electrophysiology

Sedation threshold.—The electroencephalograph has been utilized by Shagass (45) to detect varying degrees of sensitivity of patients to sodium amytal and, as a result, an objective test known as the sedation threshold has been developed. The technique consists of the intravenous injection of the barbiturate at a rate of 0.5 mgm./kg. every 40 sec. while recording the frontal EEG simultaneously. This shows a marked increase in fast activity (15 to 30 c./sec.) with a gradual increase in amplitude which, when measured, yields a characteristic sigmoid curve. The end point is the amount of sodium amytal required to produce the inflexion point on this curve. It corresponds roughly to the quantity required to produce slurring of speech. Application of this test to 750 consecutively studied cases (46, 47) yielded the following findings. In anxiety, in psychoneurotics and controls, the amount of barbiturate required to produce the end point increased with the number and intensity of manifest symptoms of anxiety; that is to say, the sedation threshold (S.T.) increased. It was also found to be high in nonpsychotic subjects showing obsessional personality traits such as excessive perfectionism. Low thresholds were found in hysterics with conversion symptoms or overdramatization. The hysterical obsessional continuum was found to be closely linked with the introversion-extraversion dimension of personality (48) as described by Eysenck. In psychotic patients the S.T. was not related to anxiety so much as to impairment of ego functioning, being lowest in those with the greatest loss of contact with reality. The presence of psychotic symptoms in schizophrenics for a year or more was associated with an increase in the S.T. compared to acute cases (47). This test also aids in the differentiation of neurotic from psychotic depressions, the S.T. being high in the former. It was found also that the test had prognostic

value with respect to the outcome with electroshock therapy, those with a low S.T. having the better chance for improvement (47, 49). The implications of this work for psychological and neurophysiological theory remain to be fully understood, but the fact that an objective measure of a drug's activity on the nervous system has been shown to be related to personality factors both as to mood and organization is of first rate significance.

Depth electrography.—A number of investigators in recent years have obtained electrical recordings from the depths of the human brain by means of chronically implanted electrodes. This approach is of great interest to psychiatry because it permits a correlation of previously unknown electrical signs of brain activity with ongoing behavior. Heath's integrated approach to schizophrenia in which he utilized deeply implanted electrodes (50), commented on by Kolb two years ago (51), has provoked considerable interest. It has been summarized more recently (52). In brief, his work suggests a facilitatory circuit in the so-called septal area, anterior to the hypothalamus, from which abnormal spiking was recorded in schizophrenic patients, the process remitting with disappearance in psychotic behavior and becoming exaggerated with emotional arousal. Stimuli to this area caused behavioral alerting and blood chemical changes like those produced by adrenocortical activation.

Sem-Jacobsen and his colleagues (53) recorded from a large number of contacts in the brain and found widely differing activities from electrodes separated by only a few millimeters. The rhythms were divisible into three groups: (*a*) those consistently present in all patients; (*b*) those appearing in response to physical or mental activation or to induced physiological changes; and (*c*) those appearing intermittently in a limited number of patients. The intermittent electrical activity observed in psychotic patients is of greatest interest. They found high voltage paroxysmal rhythms in 34 of 60 chronically psychotic patients who had normal scalp EEG's and no clinical symptoms of epilepsy. In the frontal lobe rhythmic waves of 1 to 3 c./sec. in episodes lasting 30 sec. to 10 min. were observed. An extremely hallucinated chronic psychotic frequently argued rather loudly simultaneously with the appearance of high voltage slow waves in tracings from the ventral median portion of the frontal lobe. Episodes of high voltage waves with spike forms were also noted in some tracings from temporal parietal regions. A female schizophrenic patient who started to talk delusionally showed in the first part of the depth recording a few irregular waves, then high voltage discharges, typified by spikes and waves from one contact with synchronous high voltage activity building up in other regions, such as the temporal lobe, and arrhythmic waves of 2 to 4 c./sec. in the frontal lobe. As classic focal spikes appeared she argued loudly, became flushed, then quiet. The discharges simultaneously diminished in voltage, and suddenly disappeared. The whole episode lasted three minutes. High voltage

activity from what appeared to be the main focus was not much reflected in neighboring contacts, but unspecific synchronous discharges were recorded in the ventral median portion of the frontal and temporal lobes.

Sem-Jacobsen's observations suggest the possibility of a relationship between disturbed psychotic behavior and electrical discharges of the type which we have learned to call epileptiform when recorded in the scalp EEG. He also suggests that it may be necessary to distinguish between schizophrenic patients who have paroxysmal slow activity in their depth EEG's and those who do not. It is interesting to relate these observations to evidence which Heath and his associates have provided, showing that extracts from schizophrenic body fluids produce epileptiform-like discharges in the subcortical EEG in animals. It seems that there may be some reason to believe that a significant segment of schizophrenic disorder depends for its form upon the paroxysmal activity of subcortical structures.

Sem-Jacobsen and his co-workers (54) have also employed the patient with implanted electrodes as a preparation for study of the effects of hallucinogenic agents, mescaline, LSD 25, and adrenochrome. Three schizophrenic patients who were studied showed increased paroxysmal activity after mescaline or LSD 25 orally. In two patients with epilepsy these drugs had a quieting effect on the spike and sharp wave foci in depth recordings. Adrenochrome in two patients with schizophrenia produced an increase in paroxysmal activity. Activation of the temporal depths by mescaline and LSD 25 in one patient appeared to coincide with a period of active auditory and visual hallucinations. Double spikes appeared near a region from which a similar discharge had been found in the previously reported patient during spontaneous hallucinations without any drugs. Chlorpromazine intravenously reversed these effects and the authors believed that it may have a possible mode of action centered in the temporal region. As adrenochrome failed to produce clinical and electrographic changes similar to those of mescaline and LSD 25, the authors felt that it was probably not involved in mediating the action of mescaline and LSD 25, contrary to previous hypotheses.

Taraxein.—In continuation of the work already referred to, on the finding of abnormal discharges from electrodes placed in the septal area of schizophrenics (52) and on epinephrine oxidation (41), Heath and his associates have prepared an extract from the serum of schizophrenics which they thought on theoretical grounds might elicit physiological changes (55). When injected into monkeys the ceruloplasmin fraction of schizophrenic serum elicited mild behavioral changes, reducing the level of awareness described as similar to incipient catatonic symptoms. Extracts from the blood of normals did not do this. As the authors proceeded they found a serum fraction in schizophrenic blood apparently not present in normal serum. They have named the active fraction "taraxein" from the Greek

taraxis meaning confusion, or disorder of the mind. When this fraction was suitably prepared and administered to the monkeys the behavioral changes were much more profound, the animals appearing dazed, out of contact, and catatonic. Associated with these clinical changes were clear-cut alterations in EEG tracings, especially from the septal area. These showed essentially the same characteristics as recordings from schizophrenics. The specific EEG changes constituted the key information in making the cross-interpretation from animals to man. Full details of the extraction of the pooled schizophrenic serum are given in this paper (55). It was found that 400 ml. of serum had to be processed to create a reaction in the host. The only method for determining activity of the material was on monkeys with implanted electrodes.

Experiments with human subjects included the administration of taraxein on 17 occasions to nonpsychotic volunteers and on one occasion to a schizophrenic in remission. All developed symptoms like those seen in schizophrenia, such as blocking with fragmentation of thought, decrease in contact and animation, feelings of depersonalization, and posturings reminiscent of catatonic states. It did not seem to matter what category of schizophrenia the serum was derived from. The symptomatology in the cases receiving taraxein approximated the characteristic picture of schizophrenia much closer than that elicited by LSD 25. The latter agent produces manifestations more typical of a toxic psychosis, such as disturbances of perception and autonomic stimulation. This work has aroused much interest and, as with any novel approach, criticism. Its further development will be keenly watched for it may well represent a real breakthrough on the schizophrenia front.

Therapy

The interest in therapy has been largely concentrated in the past year on the development and application of the new psychopharmacological agents. Since these will be specifically dealt with elsewhere in this volume no attempt will be made to do so here. Older therapies have been subject to more critical evaluation than before and two such reports will be summarized. They show the increasing trend to consider the importance of interpersonal relations in a therapeutic situation.

Insulin.—Conflicting opinions regarding the value of insulin coma therapy and the nature of the therapeutic effect have been discussed briefly by Boling, Ryan & Greenblatt (56) in a preliminary report on the comparative results of deep and light coma treatment in 73 schizophrenic patients. Thirty-four cases were subject to deep coma in which absence of pain reaction and lid response occurred, and 39 cases received light coma defined as early second stage and showing sufficient disorientation so that patients could not differentiate between the two types of therapy. Evaluation was

by the chief of service, head ward nurse and, in 41 instances, by the Rorschach test. By the criteria used no difference was found between the results of the light and deep insulin coma. This tends to support the contentions of those who believe that it is the psychological effects of intensive nursing care in the insulin treatment situation rather than the physiological effects of the insulin which accounts for improvement. Another group of workers, impressed by the inconclusive evidence for the nature of the benefit deriving from insulin treatment of schizophrenia [Ackner, Harris & Oldham (57)], have performed an experiment designed to avoid fallacies evident in some previous work with regard to selection of patients, insulin coma technique, assessment of outcome, and use of controls. Schizophrenics aged 15 to 40 with a psychologic history of less than a year, were randomized according to sex and diagnostic category into two groups, one receiving standard insulin coma therapy and the other, treated under identical conditions, getting oral barbiturates designed to give an equivalent amount of sleep. The results of treatment for the first 25 matched pairs followed up at the end of six months showed no significant difference in the outcome whether unconsciousness was produced by insulin or barbiturates. It was pointed out that common to the two groups was the experience of a powerful group influence and increased medical and nursing care in a dependent nurturing situation. This might be called anaclitic therapy and suggests that restoration of lost human relationships is more important than any specific effect of the insulin coma regime.

Heredity

Outstanding conferences and contributions pertaining to genetics and eugenics have been succinctly reviewed by Kallmann (58). These reflect an increased interest in the place of studies of human genetics in psychiatry, which is particularly well exemplified by the papers given at a symposium of the American Psychiatric Association and reported in the December, 1956, number of its journal.

Recently published twin data appear to be highly significant. Kallmann & Roth (59) point out that this shows relatively the same difference to exist for two-egg and one-egg co-twins of schizophrenic index cases for preadolescent schizophrenia (17.1 per cent and 70.6 per cent) as for adult schizophrenia (14.7 per cent and 85.8 per cent). It would seem, therefore, that the childhood manifestation of the disease is a product of the same genotype (gene-specific deficiency state) as for the basic symptoms in the adult form. In endeavoring to appraise environmental influence, these workers state that of all the normal co-twins and siblings, 64.8 per cent came from inadequate homes which produced the schizophrenic index case.

The articles on genetics in the volume of the *Association for Research*

in Nervous and Mental Disease (60) though almost four years old still represents one of the most available definitive publications in the field.

Psychiatry as a field for research and practice permits many approaches. These in the past have often been so different that it was difficult for workers to understand each other. This sectarianism is dissolving with the development of techniques and points of view which renders each area understandable, at least in part, in terms of another. In all probability certain aspects of psychiatry will remain esoteric, for mental phenomena have to be dealt with in terms peculiar to mind and not expressible in terms of other bodily units.

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DRUG ACTIONS UPON THE BRAIN "PSYCHOPHARMACOLOGY"[1]

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This brief report inaugurates a new section in the *Annual Review of Medicine* made necessary by a recent explosion of interest, professional and otherwise, centered upon the phenomena of "mood alteration" by drug administration. Such deliberate tamperings with the "mind" should elicit no surprise, for all man's medicaments (even his food and drink to some degree) induce in him quietude, sleep, stupor, relief of pain, exhilaration, and the like. Clearly, these alterations in states of awareness rely upon actions which drugs exert directly or indirectly upon the nervous system. The newest agents of this kind are said to make tranquil the harassed or obsessed patient. So keen, apparently, is the demand for tranquility that by recent estimate (25) 3 of every 10 prescriptions now dispensed are for "tranquilizers."

As do most explosions, that referred to above has resulted in an illuminating flash of brilliance, a promising excavation into the mountain of ignorance and an exceptionally large amount of flying rubble. So extensive is the literature kicked up by this blast that even a cursory review would require volumes rather than pages. Despite the phenomenal number of reports available, however, factual information concerning behavioral effects, dosages, indications, and limitations of these medications is limited or conflicting, and evidence concerning their precise mode of action is essentially nonexistent.

To explore the uses of "tranquilizers" it is necessary to understand the neural mechanisms upon which these (and a host of other) agents act. During the past 10 years, more than at any other time in history, information has become available linking brain function with various manifestations of alert mentation both in animal and man. Examination of these neural mechanisms is highly pertinent, therefore, to the topic under discussion. Hence, this appraisal of "psychopharmacology" will review the problem under three main topic-headings: (*a*) brain mechanisms of consciousness; (*b*) drug-induced modifications of mental activity; and (*c*) tranquilizing agents.

BRAIN MECHANISMS OF CONSCIOUSNESS

Specific and Unspecific Neural Systems

Currently it is popular to recognize two principal sensory systems in the brain, one "direct" or "specific" and the other "indirect" or "unspecific" (22). In the former class, extensively studied for decades, are the great

[1] The survey of the literature pertaining to this review was concluded in June, 1957.

lemniscal fillets each of which conveys signals characteristic of a single modality of sensation from receptor to a precise, individual zone in the cortex of the brain. These fiber tracts, which comprise the visual, somesthetic, auditory, visceral, proprioceptive, and olfactory systems, are arranged peripherally around a central core of reticular substance as they course cephalically through the brain stem. Until recently, the functional significance of this central brain stem area, called the reticular formation, was unknown. Now it has been identified as the seat of the principal integrating system of the brain which, by virtue of its manifold functions and widely dispersed ramifications, has come to be known as the "unspecific" Reticular Activating System (RAS) (42).

The RAS is called unspecific because its cells are capable of responding equivalently to impulses traversing each of the specific sensory lemnisci. Moreover, these cells can be thrown into action by signals emanating from certain cortical loci, principally those usually described as association areas, from the cerebellum, and from the basal ganglia. When so activated from these diverse sources, the RAS sends neural energy showering cephalically to widespread areas of the brain and caudally to motor and sensory centers in the medulla and spinal cord.

Functions of the Reticular Activating System

Arousal.—This wonderfully complex RAS has many functions, principal among which is the mediation of mechanisms which arouse the organism from sleep to wakefulness (47). It is easy, for example, to arouse a normally sleeping monkey by applying a small electrical current to the RAS through an electrode implanted within it (55). By contrast, destruction of the RAS, either experimentally in animals or accidentally in human beings, results in complete permanent coma (21).

Motor controls.—The RAS is also known to contribute critically to motor mechanisms. In all probability it is the seat of the hitherto ghostly "extrapyramidal" system (43) for, by stimulating different parts of it, movements and reflexes are either enhanced or inhibited. Additionally, a tremor comparable to that seen in Parkinsonism can be elicited experimentally by reticular stimulation (61).

Autonomic balance.—Most of the autonomic "centers" are known to be coextensive with various parts of the reticular formation, hence this region of the brain is vital to maintenance of vegetative balance. All manner of changes in blood pressure, respiration, gastrointestinal function, temperature control, pulse, etc., are induced experimentally by stimuli applied to the RAS. Moreover, master control of the endocrine system resides in the cephalic portion of this central brain stem structure, for the pituitary gland is now known to become activated by hypothalamic excitation (51).

Emotional stability.—Closely related to the function of autonomic control is reticular participation in emotional stability (1, 49). The brain stem structures comprising the RAS are intimately and reciprocally connected

with phylogenetically ancient rhinencephalic structures [e.g., the hippocampus, amygdala, septal region, and limbic cortex (2)]. Undoubtedly, through these circuits course the influences which add emotional coloring to responses.

Sensory control.—The recent discovery that the RAS controls reception and conduction of all sensory signals in the nervous system has opened an exciting new area for speculation and investigation. A subject can perceive or attend at one time only to a few of the billions of signals which clamor for dominance at every moment. Were there no controls to permit the brain to accept some stimuli and reject all others, utter chaos would ensue; perhaps such a condition underlies the development of certain forms of mental deterioration. Now it is abundantly clear that the RAS, in addition to its other duties, serves as control center for the sensory functions of the nervous system, for impulses conducted in primary sensory systems are inhibited or enhanced by appropriate RAS activation (28, 31).

Reticular Activating System Integration

These several functions of the RAS are by no means independent of each other but rather are so interrelated as to be inseparable. It is impossible, for example, with an electrode placed in a single point within the RAS to stimulate without eliciting variously in combination: wakefulness; change in blood pressure, respirations and pulse; secretion of trophic substances by the pituitary gland; initiation or inhibition of movement and alteration in signals conducted by primary sensory systems (5). In this integration one can see clearly the basis for pattern responses which are so vital to normal brain function. It is logical, for example, for a stimulus to awaken the subject and at the same time to inaugurate bodily changes which are appropriate to the wakeful state. It would seem that the RAS is a central structure in the mediation of these integrating neural mechanisms.

Neurohumoral Reticular Mechanisms

The previous discussion has indicated that the RAS is excited to activity by nerve impulses reaching it from all sensory systems, cortex, rhinencephalon, basal ganglia, and cerebellum. Recently attention has been focused upon the fact that this brain stem area is also responsive to excitation mediated by humoral rather than neural inputs (8, 13).

For years it has been known that at least one activity of the RAS—the mediation of autonomic control—is energized humorally. Chemoreceptors in the medulla were shown to be sensitive to circulating CO_2 in regulating cardiovascular-respiratory balance, and blood O_2 levels were found to exert comparable controls reflexly through receptor systems in the great vessels.

Recently it has been shown that additional functions of the RAS are energized by these humoral mechanisms not only through variations in CO_2 and O_2 concentrations, but also in response to action of other circulating substances as well. Arousal is induced by administration of acetyl-

choline (as well as by cholinergic and anticholinesterase drugs) and of epinephrine (as well as by adrenergic drugs) through action directly upon the central brain stem as well as upon structures representing cephalic extensions of it (9, 13). In addition, epinephrine administration has recently been shown to activate hypothalamic-pituitary mechanisms responsible for the stress reaction (51). Moreover, caudally oriented influences of the RAS are equally sensitive to humoral excitation for reflex activity (13) as well as cortically induced movements (56) are altered by administration of adrenal medullary substances.

It is clearly evident, therefore, that arousal together with all of the attributes of mind and body which normally accompany alert wakefulness are subject to controls and modifications exerted by circulating substances—metabolites, hormones, or drugs—as well as by sensory signals. Upon this framework of information the actions of drugs which distort mental processes can now be examined.

DRUG-INDUCED MODIFICATION OF MENTATION

The Anesthetic or Soporific State

For decades it has been taught that anesthetic agents act upon the nervous system first by depressing the cortex and, as higher concentrations of the drug are administered, subsequently by suppressing subcortical structures, brain stem, and medulla in regularly descending order. Recent physiological data will not support this proposal and current concepts of drug-induced stupor have required considerable modification. Now it is evident that most anesthetic drugs exert their effect principally by selective action upon the RAS (4, 23). By contrast, drugs which induce an excitant effect upon behavior and function are known to increase reticular activity and, through this excitation, to activate the cortex (4, 9).

In contrast to anesthetic action, the effects of "mood-altering" drugs upon the nervous system are not yet well understood and controversy rages concerning data that are available. These agents, however, must act in some way upon the RAS mechanism for the neural processes described are essential to normal, alert consciousness. It is appropriate here to say only that psychotomimetic drugs are thought to augment (and probably distort) reticular activity by increasing sensory inputs to the RAS (14). Conversely tranquilizers tend slightly to diminish reticular function.

Psychotogenic Agents

For centuries primitive peoples have known that ingestion or inhalation of certain herbs, yohimbine, marijuana, peyote, muscaria, hashish, opium, cocoa, etc., would cause, temporarily, remarkable distortion of their mental processes. Now it is known that the majority of these mind-distorting drugs have comparable chemical structures or at least contain common linkages. Many are alkaloids which possess an indole or indole-like fragment which is presumed to be the active principle (40).

Countless references have been made to the fact that the mental phenomena induced in subjects by administration of these agents exhibit remarkable similarities to symptoms displayed by schizophrenic patients. While this comparison requires qualification, transient psychoses of drugged individuals have led to speculation that disordered metabolites, possibly even indole amines, are responsible for some, if not all, organic psychoses (17). It is probable that this centering of attention upon possible toxic etiologies of mental disease will prove to be the greatest contribution made by investigations employing psychotomimetic agents. At least it is unlikely that induced schizophrenic-like symptoms will be found to have therapeutic value (40). The lead is well worth examining and considerable scrutiny has been given it in the recent past.

It has been suggested that psychotomimetic drugs elicit an effect by acting upon cerebral synapses rather than upon anything so universal as oxidative metabolism (35). Moreover, it appears that anesthetic drugs which affect the nervous system act more efficiently against synapses than upon neurons (39). As transmission of excitation or inhibition at synapses is mediated by the elaboration of "transmitter" substances, it is evident that altered function elicited by drugs relies upon their ability to modify the effectiveness of these humoral agents or their metabolic precursors. For decades two principal excitatory transmitter substances, acetylcholine and epinephrine, have been recognized in the peripheral nervous system. Now it is clear that these same two substances, or agents very much like them, subserve a similar function in the central nervous system. One of them, epinephrine, has received most of the recent attention regarding induced psychotogenesis.

While epinephrine itself is found in the central nervous system, an epinephrine-like substance serotonin (5-hydroxytryptamine) is currently being postulated as a mediator of central synaptic transmission. It has been suggested that abnormal products of epinephrine metabolism are responsible for schizophrenic-like symptoms since administration of substances such as adrenochrome or adrenolutine elicit these effects (34). Similarly, Woolley & Shaw (62) propose that distorted metabolism of serotonin underlies psychotomimesis. Agents such as lysergic acid diethylamide (LSD), yohimbine, mescaline, and the like, exhibit indole linkages comparable to those in serotonin, suggesting the possibility that the psychotogenic drugs disorganize normal synaptic transmission in the brain. Attractive as these proposals may be, evidence is still conflicting (24, 54) or at least insufficient to establish them (26).

Additional evidence implicating disordered "transmitter" chemistry in the genesis of drug-induced psychoses stems from the observations of Purpura (52) who found that LSD selectively operates against neural systems which contain synapses of the "axodendritic" type contained in the RAS. In addition, Marrazzi proposes that serotonin and epinephrine-like substances exert inhibitory effects upon synapses (45). Since epi-

nephrine administration is known to elicit arousal, its action might be thought of as "excitatory"; that it also activates "inhibitory" synapses creates a seeming paradox which remains inadequately resolved.

Clinical Effects of Psychotomimetic Drugs

It is improbable that two even closely related drugs act exactly alike, hence various psychotomimetic drugs doubtless exhibit wide diversity in the manner in which they affect the nervous system. Atropine in large doses, for example, induces mental changes probably by acting upon cholinergic rather than adrenergic systems, and some of the so-called mood-altering drugs have cholinergic blocking properties. In general, however, psychotomimetic drugs have similar actions and the effects of the ergot derivative LSD-25 can be examined as a prototype of most other similar agents.

Rothlin has divided the effects of LSD administration into four major categories (54). First, and most important to this discussion, is the effect upon psychic function. Moreover, the drug acts upon somato-motor centers and upon brain stem autonomic loci. Finally, a peripheral action principally upon smooth muscle is exhibited by the drug.

Particularly characteristic of the psychic reactions induced by LSD is the transient development of a "schizoid" state. Some modification of mood is usual; commonly there is excitation which may be associated either with euphoria or depression. Hallucinations frequently appear; usually these involve optic phenomena but auditory hallucinations also occur. Depersonalization is a common reaction following LSD ingestion although the degree to which this phenomenon is experienced varies considerably in different subjects. That true depersonalization occurs has been challenged (14), for test subjects are almost always aware that their symptoms are unreal. By contrast, schizophrenics exhibit loss of insight. Altered sensitivity to environment contributes to abnormal mental phenomena in LSD test individuals, for Elkes' subjects were adversely effected by relative isolation from sensory stimuli. Comparable but less extensive distortions in mental reaction have been described by Hebb (29) and by Lilly (41) in normal subjects who were isolated from environment contact.

It is probable that schizoid responses to LSD ingestion indicate modification of rhinencephalic function, since Baldwin's (6) chimpanzees displayed abnormal affective behavior only when their temporal lobes were intact and appeared uninfluenced by the drug following temporal lobectomy. Furthermore, Monroe *et al.* (46) have seen clinical EEG abnormalities, and Killam *et al.* (38) described prolonged seizure discharge in rhinencephalic structures following administration of LSD in animals. Comparably, the automatic behavior and rage responses of psychomotor epileptics is now known to be associated with rhinencephalic discharge patterns.

Autonomic effects of LSD intoxication are brought about by stimulation of medullary and mesencephalic reticular centers which control visceral

phenomena. These changes are mydriasis (in animals), rise in body temperature, hyperglycemia, piloerection, tachycardia, lowering in blood pressure, and respiratory depression. Rothlin (54) has called attention to the sympathicotonic character of these autonomic effects and considers them the antithesis of sympathetic depression produced by reserpine.

Motor symptoms of LSD intoxication, usually resulting from ingestion of large amounts of the drug, are occasionally present in the form of ataxia or spasticity. Sensory effects, such as distorted but heightened sensitivity to perceptive experience, are common (15). Doubtless, these sensory-motor effects of LSD ingestion result from central action of the drug as do symptoms referable to the autonomic nervous system. The reticular systems would appear to be the logical place to search for these actions since caudally directed reticulospinal influences are known to be capable of modifying motor, sensory, and autonomic function. Physiological evidence on the subject is still meager but available data support this proposal. Peripherally, LSD exerts a pronounced antagonism to the stimulating action of serotonin on smooth muscle (24) and a week adrenergic blocking effect.

TRANQUILIZING AGENTS

In discussing this topic some initial effort should be made to classify drugs which exert a mood-altering effect upon man. Pfeiffer (50) lists nine subheadings (according to induced behavioral change) into which drugs acting upon the central nervous system can be grouped; "mood-altering" drugs are included in five of these. Berger (7) groups tranquilizing agents into four subdivisions according to their chemical structure: (*a*) phenothiazines (chlorpromazine etc.); (*b*) reserpine alkaloids; (*c*) diphenylmethane derivatives (azacyclonol); (*d*) propanediols (meprobamate). Physiologically, however, the first 3 groups (phenothiazines, reserpine alkaloids, and diphenylmethanes) can be considered together since they seem in general to have similar properties. In addition, most of them are said to affect the autonomic systems, to potentiate barbiturate action, and to depress conditioned responses (26). Propanediols apparently act differently, for they have none of the above-mentioned actions of other tranquilizers but relax striated muscles by depressing CNS interneuron action (7, 30) and probably their tranquilizing properties can be attributed to this action. Moreover, perhaps stimulant drugs should be included as a third major division in this discussion for these agents are used frequently to alleviate depression.

Gerard (26) suggests that the first major group (phenothiazines, reserpine alkaloids and diphenylmethanes) is useful in treatment of the psychoses. The propanediols, he feels, are of "little use" in psychotics but are more helpful in quieting the larger population of neurotic individuals. The third major group of mood-altering drugs mentioned would seem to apply to problems of aging or to certain narcoleptic or depressed individuals (18).

In the available space it will be possible only to epitomize information concerning the uses, contraindications, modes of action, etc., of these drugs. The reader is urged, therefore, to consult the more extensive treatises and symposia on various aspects of clinical use, many of which have been referred to herein [cf. (3, 7, 9, 10, 11, 36)].

Chlorpromazine

A discussion of chlorpromazine will serve to describe actions and uses of the phenothiazine drugs since this agent is the oldest and probably still most widely used. Chlorpromazine administration is said to reduce anxiety, tension, and psychomotor hyperactivity, and to control disturbed behavior in psychotic patients thus making them more amenable to treatment (27, 44, 60). Also, the efficiency of this agent in controlling nausea and vomiting has recommended its use in treating these symptoms. Neurodermatoses, intractable hiccoughs, postalcoholic states, and narcotic addiction are also said to be alleviated by chlorpromazine, and the drug is known to potentiate sedatives.

Complications are not common but when they occur require recognition and attention (27, 44, 60). Bone marrow depression and jaundice, while rare, demand immediate discontinuation of the drug. Less critical symptoms, perhaps, are fatigability or somnolence, Parkinson-like tremor, dizziness, variation in body temperature, constipation, galactorrhea, and weight gain (60).

Physiological investigations into sites of action of chlorpromazine have been thoroughly reviewed (3, 33, 38), but that of Killam is particularly complete (36). She states that autonomic effects may be attributed to a mild peripheral adrenergic blocking activity but more particularly to central depression of the brain stem. Depression of hypothalamic sympathetic centers (33, 48) has also been proposed. Clearly, such depression is adequate to explain gastrointestinal, cardiovascular, respiratory, and temperature-regulating depressions. Explanation of the tranquilizing phenomenon, however, is much more difficult. Depression of the RAS (33, 59) or hypothalamus (33) has been incriminated. Hiebel and associates (32) support this contention, believing humoral activation of the RAS to be impaired. By contrast, Killam & Killam (37) and Bradley (9) find this RAS involvement considerably less extensive and more subtle than that which occurs following, for example, barbital administration. Partial blockade of the arousal response occurs principally in the thalamic region and enhanced reticular inhibition of sensory inputs may play a dominant part in induced tranquility (37).

Reserpine

The effects of administration of the Rauwolfia alkaloids are strikingly like those which follow dosage with phenothiazine agents yet the mode of action of these two agents is widely divergent. A glance at the chemical

formula of reserpine (Fig. 1.) will indicate that this substance contains an indole linkage rendering it similar to psychotomimetic drugs, in particular to yohimbine. This similarity has prompted suggestions that the effects of reserpine administration are due to an antimetabolite relationship with serotonin (10, 57) but these efforts have not been uniformly successful (24).

As noted above, the effects of reserpine administration are similar to those which follow ingestion of chlorpromazine. A principal use has been to treat mild, labile hypertension. Some other indications for use of these drugs

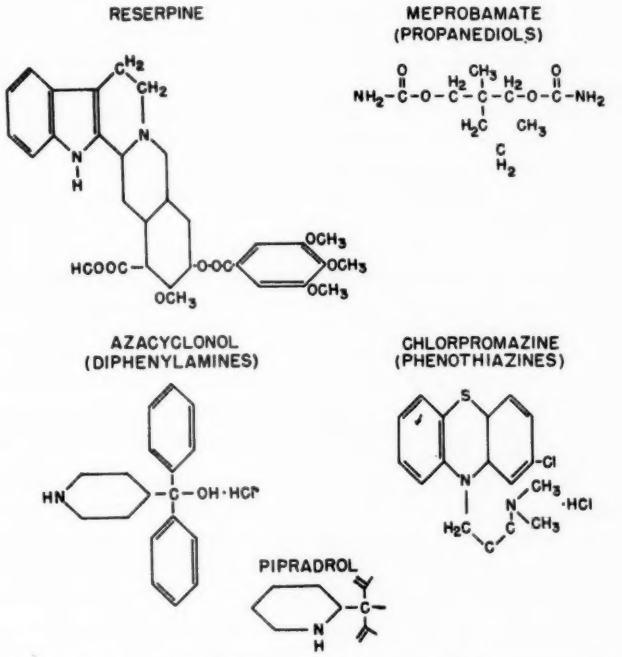

Fig. 1. Four classes of tranquilizing agents are commonly recognized. Chemical structures of these drugs are diagrammed here.

are anxiety or tension states, adjunctive therapy for somatic disorders and for psychomotor hyperactivity, and disturbed psychotic states (to increase accessibility) (11, 20, 60). Pediatric or geriatric behavior disorders have also been treated by reserpine but caution should be exerted in their use in pediatric therapy. Toxic reactions reported (27, 60) are nasal stuffiness, weight gain, diarrhea, and postural hypotension. Occasionally, dryness of the mouth, increased gastrointestinal activity, and fatigue are noted. Of

rare occurrence but greater importance are acute peptic ulcerations, severe mental depressions and seizures in susceptible people. Skin erruptions occasionally develop as do Parkinsonian tremors.

The manner in which reserpine exerts its effect is even less apparent than is the mechanism which mediates the action of chlorpromazine. Brodie suggested that liberation of serotonin (10) is a principal factor in the tranquilizing powers of reserpine but this has not been fully substantiated. Reserpine antagonizes some peripheral actions of serotonin (12) and a similar effect may occur in the brain (45). The nature of the symptoms induced by this drug suggests that some modification in the RAS function underlies its action, although suprisingly little alteration in arousal mechanisms has been uncovered (38). Hypothalamic depression has been suggested as a selective action of this tranquilizer (48, 53), and rhinencephalic action would appear possible because of reserpine amelioration of sham rage. By contrast, this drug appears to augment experimental seizure activity in the visceral brain rather than to depress it (36).

In short, the manner in which reserpine acts upon the nervous system remains a mystery.

Azacyclonol

This agent, a relative newcomer to the list of tranquilizers, is noteworthy not only because of its ataractic action but because it is the gamma isomer of a stimulant, pipradrol (Fig. 1) (similar to amphetamine, Fig. 2). Such a slight change in the structure of a compound is evidently capable of altering its action from sedative to stimulant. Azacyclonol is said to induce a state of quietude in a manner comparable to other tranquilizers mentioned, hence to have somewhat similar indications (16, 60). It is said also to have low toxicity (60).

As yet, lack of experimental data makes enlightened speculation impossible concerning the site of action of this drug. Fabing (16) has found that its administration blocks LSD or mescaline-induced psychoses. The experimental and clinical evidence obtained by Monroe *et al.* (46), however, was less conclusive concerning azacyclonol blockade of LSD.

Meprobamate

This agent appears to have an action different from most other tranquilizers. It is similar in structure to mephenesin, a muscle relaxant drug, and shares this relaxing quality. Additionally, it appears to have sedative actions. These properties, coupled with fairly long action and low toxicity, have recommended its use principally in conditions dominated by psychological or muscular tension or both (26, 60). These actions are considered to be exerted exclusively upon the central nervous system and to be the result of selective interneuron depression (7, 36).

Central Nervous System Stimulants

A brief mention concerning the use of stimulants is included here since

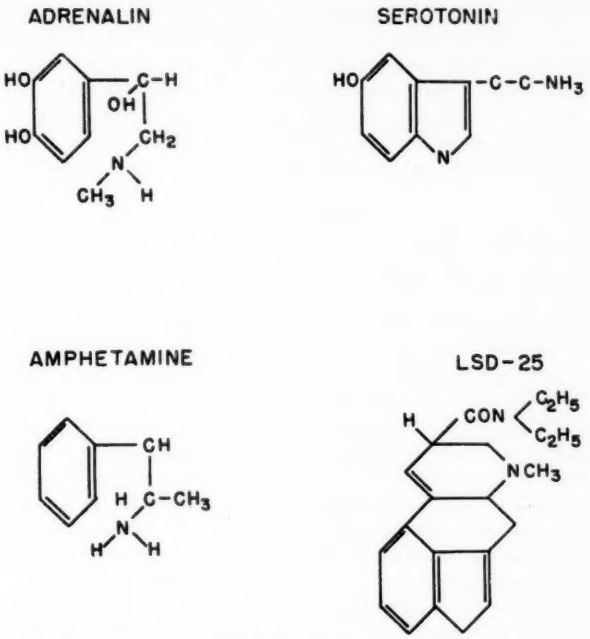

Fig. 2. Chemical structure of drugs which induce psychotic-like behavior are indicated here. Note indole-like linkages which they contain. See text for more complete discussion.

these agents are in a broad sense also "mood-altering," and since they have been used on occasion to combat spontaneous or drug-induced depressions. Amphetamine has had the longest and most widespread use, its stimulant qualities having been employed in treatment of behavior problems in children, in certain types of depression, and in narcolepsy (36). Its central action is elicited by lowering the threshold of excitability of the reticular formation (4, 9) and its use may lead to hyperactivity, often sleeplessness, and anorexia. Moreover, it has a potent peripheral activity in the form of sympathomimetic stimulation resulting in blood pressure elevation, vasoconstriction, rapid pulse, etc.

Recently, another class of stimulants has been investigated and found promising. These agents are pipradrols which are somewhat similar in structure and in action to amphetamine but without the appetite loss or pressor effects induced by the latter drug. One of these is the optical isomer of azacyclonol, a tranquilizer. Fabing (18) and others (58) have reported

that this agent blocks LSD psychoses and its use "has merit in some patients with schizophrenic dissociation syndromes." Another stimulant, methylphenidylacetate, also exhibits minimum peripheral sympathomimetic effects and induces central stimulation (40). Ferguson (20) found that improvement followed use of this medication in chronic schizophrenics who were deteriorated and negativistic. It has also been used to counteract drug-induced depressions such as that seen with reserpine (11, 19).

CONCLUSION

The preceding account is meant only to be a brief summary of an important new clinical discipline which has very recently developed and which gives promise of even greater growth. In order to follow this growth with enlightenment, it is necessary for the physician to examine data which commonly do not enter his usual field of contact, material, for example, from the neurophysiology, pharmacology, and biochemistry laboratories as well as from diverse clinics. In the truest sense, this new field of "psychopharmacology" is, indeed, an interdisciplinary approach to a study of disease. That the study it explores embraces the vast area of mind-brain relationship, both normal and disordered, clearly justifies the attention it is receiving. These investigations cannot help but be enlightening, but present knowledge is so limited that considerable caution must still be exerted in accepting conclusions concerning drug indications, effectiveness, and modes of action.

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CLINICAL EVALUATION OF DRUGS[1]

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A complete review of the material subsumed under the above title and published during the past year or two is impossible within the space limitations of this article. We have, therefore, chosen to discuss a few general topics in this area which have aroused recent interest. This material can be considered as falling into three broad categories: (*a*) basic concepts of the clinical trial; (*b*) sequential design and analysis; and (*c*) estimates of therapeutic efficacy based on duration of life.

BASIC CONCEPTS OF CLINICAL TRIALS

It is a pleasant fact that more often in these days than in previous years clinical experiments are being designed and performed in a manner suggesting consideration by investigators for certain fundamental experimental concepts. The basic principles of such clinical trials are reasonably simple, founded on sound rationale, and do not require professional statistical training for their appreciation or application. These principles have been described on several occasions by different authors (1 to 4).

Of late, however, there have been some disquieting developments. The general acceptance of the word "controlled" as a complimentary adjective has fathered any number of papers dealing with experiments whose "controls" resemble the emperor's new clothes in their invisibility to the critical eye. Other highly respectable terms are used by authors with a profligate abandon which is, unfortunately, often detectable only by information other than that available in the published works. (We refer to the use of "random" to mean "haphazard," "blind" to mean "somewhat confused," etc.) Another development, in the opposite direction, consists of suggestions that the generally accepted structure of controlled experiments is faulty and requires drastic change. Some of these latter criticisms are well-taken and deserve consideration or implementation; others are mere cavil or nonsense.

The most peculiar of these criticisms is the assertion that the "double blind" technique in some way defeats the investigator and renders him unable to differentiate active from inactive drugs (5). This argument is apparently based on the observation that certain investigators are capable of discerning maximal therapeutic benefit from an "active" drug only when

[1] The survey of the literature pertaining to this review was concluded in June, 1957.

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they know what they are giving, and fail to discern such benefit when kept unaware of the nature of the medication. Reasons for this interesting state of affairs are not usually proffered (although certain explanations come readily to mind), nor is there any suggestion offered as to how one ought otherwise to control investigator bias, a proven hazard in clinical work.

In point of fact, of course, the double blind technique has been used successfully on many occasions to distinguish between useful and useless drugs of many types. It seems difficult, however, for some investigators to appreciate the following facts. First, the double blind technique (even when properly used) is only one aspect of a good experiment and is not sufficient to guarantee the quality of the total design or its application. Second, the failure of a significance test to establish a difference between two drugs does not prove that they are the same; whether or not the difference is significant, an investigator of moderate inquisitiveness will want to calculate confidence limits to see how large or small the difference might reasonably be. In this way he may find that his experiment was too insensitive to be sure of detecting the anticipated difference. (It would be to the investigator's advantage, of course, to plan his experiment in such a way as to avoid this outcome.) Finally, if an investigator already "knows" that a drug is active, and is unwilling to entertain evidence to the contrary, there is hardly any point in doing an experiment to "determine" whether the compound is better than a placebo.

A different kind of criticism of the double blind technique is that often it is not, in fact, "blind," i.e., that it is possible for patient or observer or both to distinguish a drug from placebo by some of the side effects produced by drug. This problem is hardly a new one (4), but extremists have suggested that it completely destroys the usefulness of the "blind" technique. The perfect double blind situation—wherein the active drug does nothing other than to produce the desired therapeutic effect—is admittedly a rare one and, in general, there will be a variable degree of successful deception depending on the incidence and severity of the side effects.

There are, nevertheless, some happy facts about clinical trials which negate much of this criticism: (*a*) it is rare for a drug to produce side effects in all subjects; (*b*) it is rare for a placebo not to produce side effects in some subjects; (*c*) the production of side effects (usually unpleasant) is not tidily correlated with desired therapeutic effect; (*d*) analysis can always be performed to investigate the possible correlation of side effects and therapeutic success; (*e*) coding can (and should) be done individually so that one code "break" does not bias all other subsequent observations; and (*f*) even an obviously detectable placebo can still serve as a control for the spontaneous improvement (unrelated to "suggestion") which is at times the main or sole component of the "placebo response" (4). Finally, even a partial control on subject and observer bias is infinitely better than no control at all.

It has been suggested that one solution to the above problem is to use

"active" placebos, i.e., substances which are devoid of therapeutic effect but produce side effects mimicking those of the drug under study. When available, an active placebo may be a useful adjunct to an experiment, but one is still well advised to include an "inactive" (or old-fashioned) placebo as one treatment, since it is not always possible to gurantee a priori that the drugs placed in the "active" placebo will be free of beneficial (or deleterious!) effect on the parameter under study. In many situations, one may properly be interested only in comparing active drugs (e.g., a new drug with a standard drug) rather than drug and placebo; if the side effects of the drugs compared are similar, much of the above concern will disappear.

Other critiques on the clinical trial have come from a group of English statisticians (6 to 9). Hogben and some others have been conducting an attack upon the established ritual for clinical trials which is certainly provocative if also more than a little captious. One aspect of this criticism is the demand for more detailed investigation of the nature of drug actions. It is not enough, they suggest, to show that drug A is better than drug B on the average. One is invited to ask, "For which people (and why) is drug A better than drug B, and vice versa? If drug A cures 40 per cent and drug B cures 60 per cent, perhaps the right choice of drug for each patient would result in 100 per cent cures." It may be answered that although the second question is more complex than the first, both are amenable to investigation by means of the classical clinical trial. However, one must acknowledge that many proponents of the clinical trial seem to feel that the questions to be answered must all be completely defined in advance and, furthermore, that they must be pretty simple questions. Provided that "flexibility" does not become a pseudonym for simple sloppiness, the cry for greater sophistication in clinical trials, although not entirely original, must be commended. Clinical trials are often unnecessarily inflexible in regard to dosage, duration of treatment, and other matters. There is no compelling reason why experiments can not be performed in which drug usage more closely approximates actual medical practice. For example, it has never been clear why a controlled trial cannot allow, or should not allow, individual titration of a drug for each patient.

Hogben gives considerable emphasis to the "self-controlled trial," that is, a study in which one investigates multiple responses to treatment and withdrawal of treatment "in comparable bodily states" in "one and the same individual." The "self-controlled" procedure has often been used to good advantage, but one must note a few reservations. As Hogben and Wrighton themselves point out, where responses to treatment are "irreversible" or where a patient can be studied only once, the self-controlled trial is obviously impossible. More generally, the therapeutic challenge is often quite variable in a given individual so that "each person his own control" at times becomes a quasi-meaningless charade. Furthermore, learning effects extending over a series of "treatments" and "withdrawals" may result in repeated measurements of something quite different from the untutored response to the drug

in an ordinary clinical setting. In short, there are many cases in which a comparison between different individuals may be far more useful than comparisons within individuals. Hogben & Sim suggest (9) that the investigator obtain ancillary observations as a check on variability of response. This is often (unfortunately) nothing but a pious hope, since one is frequently ignorant of the pertinent variables to be studied, or how to measure them. (The anthropometric data emphasized by Hogben & Sim are likely not to be pertinent, for example.) Assessing the functional state by relevant biochemical and biophysical tests, recording personality structure, etc., is an admirable notion and worthy of emphasis and trial, but it is easier said than done. Endless and aimless proliferation of measurement often leads to confusion rather than to enlightenment, as a glance at many of the studies utilizing psychologic measurements will clearly demonstrate.

Other of Hogben & Sim's recommendations such as the use of coding, double blind technique, and careful records, represent good but scarcely novel advice. However, the relaxed attitude toward the need for randomization is most unfortunate. The rationale for a confidence statement is completely dependent upon the assumption of randomization and, although the investigator may convince himself that his results are valid without randomization, he may find that hard experience has taught others to be less charitable.

Finally, it may be well to emphasize that schemes such as alternation of subjects, use of odd and even serial numbers, and so forth, are not the same thing as randomization and may be far from equivalent to it. A minor gain in convenience is poor payment for the loss of an objective measure of error. The fact that the experimenter cannot think of any way in which the serial number would affect the characteristic under study may be more of a tribute to his lack of imagination than to the validity of his findings.

SEQUENTIAL DESIGN AND ANALYSIS

Sequential tests in clinical trials have begun to attract attention. Although Wald's book (10) on sequential design appeared in 1947, to date only a handful of papers on the application of this approach to medical problems has been published (11, 12[3], 15, 16).

Ordinary clinical trials are presumably ended when the total number of patients reaches some number determined at the start of the trial, or at least by some decision which is independent of the results obtained during the course of the experiment. Classical tests of significance are not applicable to trials where an experiment is ended because the data obtained up to a given point strike the investigator as happily suitable for analysis. Yet on occasion there may be excellent reasons for terminating an experiment at some early point in the course of research. We are then faced with

[3] This paper and the subsequent correspondence concerning it in the same journal (13, 14) tackle the problem of consistency of response in patients in a way which would cheer Professor Hogben.

the following question: "If we want to 'peek' at our results from time to time, how can we control our peeking so that it is possible to place a correct significance value on differences observed between treatments?" Sequential analysis provides for such controlled peeking and allows one to calculate the increased differences which must be obtained in order to achieve statistical significance in the face of "peeking." These problems have been clearly and ably described by Armitage (17).

The enthusiasm for a new technique tends, in some quarters, to outrun the value of the contribution (15). Lest misuse result in discredit to a potentially valuable tool, the disadvantages as well as the advantages of the sequential technique must be considered.

The primary advantage conferred by a sequential design is the fact that, when the outcome of an experiment is clear at an early stage, it is possible to terminate and to draw conclusions with a known and predetermined risk of error. Where serious ethical considerations are involved (such as the withholding of a potentially beneficial drug from patients who may otherwise die)[4] the advantage in a scheme which permits early and secure drawing of conclusions is obvious. Likewise, if cessation of testing an obviously inferior product can be effected with known risk of error but without completing a preset number of trials, much wasted effort may be eliminated. More generally, on the average, the amount of clinical material consumed by a sequential scheme per clinical trial will be less than that required by fixed sample-size schemes.

However, sequential schemes have a number of disadvantages to counterbalance these benefits: (*a*) A sequential design is feasible only when the clinical response to treatment can be determined with little delay. If subjects can be gathered within a week but the result of treatment is observable only months later, there is no way to make use of a sequential scheme. (*b*) A sequential design will generally require considerable flexibility in administrative arrangements. If a large-scale clinical trial is to be set up it may be necessary to hire a special staff and to provide for other services. With fixed sample-size plans such needs can usually be estimated in advance with fair accuracy. By its very nature, the sequential design makes such planning difficult. (*c*) The theoretical development of sequential designs is still fairly rudimentary. At present, only a few special designs are available for use and the construction of others would involve considerable algebraic labor. The available formulas for determining confidence limits are only approximate and may require somewhat tricky and unfamiliar calculations. Eventually, further research will eliminate these objections, but at present these restrictions on the use of sequential designs are substantial. (*d*) Finally, the information which current sequential schemes provide is generally more limited and more difficult to interpret than the information provided by fixed sample-size schemes. Suppose that we are able, through a sequential design, to stop experimenting after

[4] An extremely rare situation in controlled trials, one might add.

studying only a few patients. We may then be 95 per cent certain that drug A is, in fact, better than drug B, but we will have only a crude idea of how much better. If we are really interested in the magnitude of the effect, a fixed sample-size scheme is more likely to serve our purpose. When a new drug is found to be better than a standard, a fairly good measure of the degree of improvement is almost essential and the researcher is likely to continue the experiment until an adequate assessment can be made. In this event the "sequential" feature of the original plan is really irrelevant. However, when the new treatment is found to be inferior to the standard, one may not care to see just how bad it really is, and the sequential design may then result in a considerable saving. In any case, the data provided by a sequential plan are usually less suitable for informal manipulation by the experimenter than are the data collected in a fixed sample-size experiment. If one does not expect to be content with the simple yes or no answer for which the sequential design was constructed, a fixed sample-size design may be much more satisfactory.

Estimates of Therapeutic Efficacy Based on Duration of Life

There is beginning to appear a long overdue discontent with the estimates by physicians of the duration of life in patients suffering from chronic diseases. In respect to therapeutics, an important question often asked is, "In patients suffering from X, a disease known to be capable of producing death, does treatment Y alter the life span?" (The word "alter" is used purposely here to emphasize the fact that from time to time treatments may actually *shorten* life by reason of toxic effects.) This problem is of particular importance in the area of cancer chemotherapy.

Ideally, we should like to compare two treatments by applying each to a large random sample of patients and comparing the distribution of survival times in the two groups. If the distributions differ, we should like to know how they differ and why. Because of the long survival time of some patients, the changes with time in risks from this and other causes of death, and the near impossibility of obtaining random samples of cases, the problem of estimating these distributions is extremely difficult. Without controlled experiments it is unlikely that an available group given treatment A will be at all comparable to some other group given treatment B, and comparisons between their survival distributions may therefore be quite misleading. This is remarked on in the literature with great regularity and ignored with almost equal frequency. Certainly, if we have no good data we must make the best of what we have but, unfortunately, this view is often extended to the idea that what we have may not be so bad after all. Lees (18), among others, has commented forcefully on this state of affairs.

Whether the subjects be well or poorly selected, however, we are thrown into hopeless confusion if the distribution of survival times is not estimated properly. If all subjects could be followed from treatment to death, there would be no difficulty here. However, varying lengths of follow-

up and losses from observation create a problem in estimation which is by no means trivial. The many fallacies in some commonly used indices of survival have been thoroughly explored [Merrell & Shulman (19) and Berkson & Gage (20)] and we will not go into them here. If one can assume that patients lost from observation and subjects with short follow-up are not different from other subjects, the best procedure for estimating the survival distribution is the so-called life-table or "actuarial" method. The rationale and calculations are lucidly described by Merrell & Shulman (19) and also by Berkson & Gage (20). If the assumption of no time trend is dubious, as it often is, the calculation should be applied only to those subjects treated early enough to have a substantial follow-up period available.

Assuming that we have a reasonable estimate of the distribution of survival times, it is still necessary for many purposes to introduce a single numerical index of survival. The most common index in cancer research is the "five-year survival rate." This index is not altogether satisfactory. If it is taken to represent a cure rate it is, of course, misleading. But even if this fallacy is avoided, the use of this index will often result in rather insensitive comparisons between survival distributions. Ordinarily, one might instead expect to use the mean survival time, but in cancer follow-up we find that some patients live many years, and this index will not be available until the last patient dies. A more suitable index, therefore, as pointed out by Lees (18), is the median survival time, i.e., the time at which it is estimated that 50 per cent of the patients have died. Although confidence limits for a median estimated from life table calculations have not been widely discussed in the literature, approximate limits can be calculated and, when a single index reflecting the survival distribution is desired, the median will probably be as suitable an index as any. The life table calculations can, of course, be used to compare points other than the median survival time if such comparisons seem desirable. It seems doubtful that indices based on highly complex calculations have any great advantage to offer in most follow-up problems.

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DIAGNOSTIC RADIOLOGY[1]

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The first American periodical devoted to the publication of original contributions in the field of medical radiology made its appearance as *The American Quarterly of Roentgenology*, the official journal of the American Roentgen Ray Society. The Society had been organized in 1900 but it was not until 1906 that the *American Quarterly* made its appearance. The official name of this journal has been altered from time to time to describe with greater clarity its range of scientific interest. Its present full name, *The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, was adopted in the fall of 1951.

Quite fittingly, this American journal published throughout the year 1956 in volumes 75 and 76 golden bound issues in commemoration of its fiftieth anniversary. A considerable portion of this commemorative publication falls within the present period of review and it, therefore, seems appropriate at this particular time to call attention to at least some of the excellent review articles written at the express invitation of the editor, which provide not only the current status of various important phases of diagnostic radiology, but which also illuminate the present with well-selected glimpses of the past.

If this year's annual review of diagnostic radiology has something of the flavor of a semicentennial analysis an explanation for the situation has been provided. In particular, this is true in the case of what is perhaps the most outstanding of the review articles to be found in the golden anniversary numbers. Caffey (1) who, more than any other individual, is to be credited with the creation of pediatric radiology as an important constructive component of medical radiology, has drawn from the first 60 years of pediatric roentgenology in the United States the highlights of its development and progress, presented with a supporting bibliography of 123 carefully chosen references.

THE BIOLOGICAL EFFECTS OF RADIATION

In no single year since Roentgen's discovery has there been such widespread concern and discussion in the matter of the tissue effects of radiation as in the 12 months just past. Contributors to this lively discussion are to be found in almost every walk of life for never before has there been such awareness of radiations of all sorts and never before have so many persons been directly or indirectly associated with activities in which radiations are employed. Warren (2) has studied the life span of a very con-

[1] The survey of literature pertaining to this review was concluded in August, 1957.

siderable group of physicians and has announced that there seems to be acceptable evidence that exposure to radiation over a long period of years can shorten the life of such individuals. He is well aware that the statistical data used by him cover a period of time when precautions against overexposure were virtually nonexistent, when many radiologists and their associates were subjected to exposures which would be unthinkable in this day and age. Taylor (3) has discussed the fundamental philosophy of radiation protection, and the National Committee on Radiation Protection and Measurement (4) has set forth the rationale upon which its "Maximum permissible radiation exposure to man" is based. Larsson (5), and Osborn & Smith (6), together with many other observers, have made inquiry into the magnitude of genetically significant radiation to which patients and radiologic workers of all sorts are exposed in the various activities of medical radiology. Stauffer (7) points out the particular need for awareness of the necessity for protection against unnecessary radiation among examiners and patients in the field of angiography, particularly where multiple exposures at short intervals are required. An extremely modern note, prophetic of what may be expected in the years to come, is to be found in a contribution by Ebersole (8) dealing with the radiation hazards with which the Navy had to cope in developing the USS Nautilus.

The complete answer to the extent of hazard presented by the medical employment of radiation has not as yet been found. It does seem, as 1957 passes its mid-point, that there is actually less reason for humans to become alarmed over the potential dangers of radiation in the amounts currently being used in medicine than at first seemed to be the case. Certainly it is true that the voluble discussions of the subject will have the certain effect of curtailing unnecessary exposure and devising schemes whereby necessary exposure can be held at a minimum. Already thrilling and promising advances have been achieved in the manufacture of more sensitive x-ray film, faster x-ray screens, and publication of the fact that moderate additions of filtering aluminum can produce desirable attenuation of biological effect without serious loss in the production of readable roentgenograms. Image amplification, now emerging from the experimental stage and assuming practical importance, at one and the same time offers an avenue for the reduction of radiation exposure and the possibility of even greater exposure unless the benefits of amplification are carefully guarded for there is a tendency to offset this advantage by more profligate filming and screening.

TECHNICAL ADVANCES

An interesting and extremely useful technical development of the past 15 years has this year been presented by Hodges (9) who illustrates and documents the present status of phototiming. It has been shown that the substitution of instrumentation for arbitrary conventional methods of determining radiographic exposure is not only feasible but conducive to a level of technical excellence previously unattainable. While there are limi-

tations in the matter of cost, it is comforting to know that phototiming is workable and nearly every sizable installation of radiologic equipment used in medicine will be found to have phototiming at least in its miniature chest filming apparatus. The matter of duplicating original roentgenograms of particular interest or merit can be accomplished simply and very well by the method of solarization as outlined by Deibert & Johnson (10). A very considerable improvement in the reproduction of roentgenograms by a method which permits great freedom in the matter of accentuating or suppressing radiologic features as desired is nicely set forth by St. John (11).

An intriguing concept in the development of contrast materials for medical roentgenography involves the chemical procedure of chelation. In recent months several articles have appeared describing the explorations by individual workers in this field, and progress to date is well-summarized by Shapiro (12). The interesting and promising field of fluoroscopic image amplification is comprehensively discussed by Mühleisen (13), by Schütz & Frommhold (14), as well as by Bezold, Feindt & Pressler (15).

The use of isotopic materials as substitutes for conventionally produced x-rays is gradually making headway [Burke (16); Krebs & Kereiakes (17)], while Friedell, MacIntyre & Rejali (18) have borrowed the scanning methods used in the study of the thyroid for mapping of the liver, and Zacks (19) has used isotope perfusions for clinical studies of cardiac physiology.

SKELETAL AND NERVOUS SYSTEMS

Procedures related to the analysis of the status of osseous structures and the central nervous system which is protected by bone represent, in the aggregate, a considerable portion of the annual efforts of diagnostic radiologists—more than one-third, in fact. The proportion of published material in this field is correspondingly high each year, and because the diversity of detailed subject material is great it is difficult to select what may properly be considered the most representative contributions for any one year. Nothing which is completely revolutionary in the way of new concepts of radiologically demonstrable disease in this field has come to light within the period here considered, although clarification of many obscure situations has resulted from critical analysis of accumulated experience. Each year a great number of individual case reports, exemplifying bizarre or unusual findings, add zest to the reading of current literature, and some of these have been included here.

Fibrous dysplasia has been a somewhat controversial subject for many years. A series of 39 examples of fibrous dysplasia involving the skull and bones of the face, and another single example in the skull exhibiting sarcomatous characteristics, are helpful in bringing a better understanding of this unusual osseous disease [Fries (20); Hobbs, Fisher & Beck (21)]. Another intriguing abnormality of bone, the epidermoid, is illustrated by Haig (22) with an example in which malignancy complicates the situation.

A clinical situation new in the experience of this writer until the past year was described in the current literature the day following that experience. A patient had been referred for examination of the temporomandibular joints to explain, if possible, the patient's inability to open the mouth more than 2 cm. No temporomandibular joint abnormality could be demonstrated, but an unusual mass of bone arising from the coronoid process on one side was seen to have formed a virtual ball socket joint with the maxilla. This unusual situation has been described by Holmes (23). Detailed examination of salivary glands by means of the introduction of opaque material into their ducts is not new basically, but Rubin & Holt (24) have presented niceties of technique which permit broader diagnostic use of the procedure. An extremely interesting use of radiologic methods to assist in the differential diagnosis of retrolental fibroplasia and retinoblastoma in infants and children depends upon the recognition of lime salt deposits within the eye as presented by Tayebi (25).

Pendergrass *et al.* (26) have contributed descriptions of useful techniques for the intimate study of the tympanic cavity and the auditory ossicles, and have commented extensively on the dependability of radiologic findings in determining the status of these minute cranial structures.

Another of the review articles discussed at the outset has great merit as a source of very valuable comment and bibliographic reference in the field of roentgenographic signs of brain tumor [Gilbertson & Good (27)]. The particular field of tumors involving the sella turcica and its immediate vicinity is most helpfully discussed and illustrated by Hanelin & Bakay (28), while a single example of large intracranial aneurysm producing panhypopituitarism is presented by Gallagher *et al.* (29). The role of cerebral angiography in the evaluation of acute brain injuries has been outlined and documented by Fasiani (30), and thrombosis of the middle cerebral artery has been discussed by Verjaal & Neyens (31).

The use of contrast material of positive density for delineation of the ventricular system of the brain has long been alluring to radiologists. A critical evaluation of the potentialities of this method of study is offered by Horwitz (32). Over the years there have been numerous warnings regarding the deleterious effects of contrast materials on central nervous structures. The nature and extent of untoward end results traceable to contrast material have been presented by Davies (33).

Several examples of migration of metallic foreign bodies have been reported in the literature during the past year. One of these involving the migration of a dislodged Smith-Peterson nail, ultimately producing a huge soft tissue cyst, has been presented by Terrafranca, Zellis & Babyn (34). Not all protrusions of intervertebral disc material into the neural canal are productive of clinical symptoms as shown by McRae (35). Fibrous dysplasia of bone sometimes involves the vertebral column where its detection is less simple than in extremity bones [Rosendahl-Jensen (36)].

From California where the disease is endemic, coccidioidomycosis affect-

ing bone in 18 patients has been reported with excellent documentation and discussion. It is of considerable interest to observe that mortality has been almost nonexistent [Birsner & Smart (37)]. As a direct corollary, the appearance and significance of blastomycosis involving bone is presented by Carnesale & Stegman (38).

An analysis of 52 examples of osteoid osteoma by Flaherty, Pugh & Dockerty (39) illustrates the many radiologic expressions of the lesion and emphasizes the characteristic common denominator by which it can be recognized. Paget's disease, most commonly observed in the cranial bones, the pelvis, and the femurs, has been observed 15 times in the jaws by Cooke (40), and solitary myeloma of bone, which is thought by some never to occur, has been reported by Russo & Brown (41) to underline further the fact that it is possible for this disease to be expressed in the form of a single osseous lesion. Schobinger Von Schowingen (42) presents a discussion of primary reticulum cell sarcoma of bone, while the radiologic features of benign chondroblastoma of bone are presented by Sherman & Uzel (43). An interesting observation based upon the radiologic survey of a single child exhibiting dwarfism has been reported by Lenk (44). He described metaphyseal dysostosis with strong evidence that, in this case at least, the abnormality is hereditary in nature. Tucker (45) has analyzed the clinical and radiologic aspects of patients shown to have complete spinal obstruction on myelographic examination. The incidence of various underlying causes is set forth.

CHEST

The employment of radiologic procedures to detect, to determine the extent and character and, on occasion, even the etiology of intrathoracic abnormalities has long enjoyed well-deserved respect and approval. In view of the great volume of published material regarding the radiologic appearance of the chest in health and disease, it is somewhat surprising that each year brings forth new concepts regarding pulmonary disease which can be demonstrated by radiologic methods, and each year ingenious radiologists describe new techniques and hitherto unrecognized or underestimated radiologic signs of significant abnormality.

The photofluorographic procedure of chest surveying, so widely used throughout the world, has often been attacked as inaccurate and, therefore, unreliable because of the fallibility of individual interpreters. A most ingenious method of assaying the actual reliability of various individuals who examine and interpret photofluorograms is described by Nielsen (46) who introduces false shadows resembling pulmonary infiltrates and thereby is able to score the effectiveness of individual observers. Combining tomography and bronchography, Juhl, Alt & Wasserburger (47) describe and discuss the occurrence and appearance of bronchiectasis in the pulmonary apices. By means of a single case report the possibility of primary bronchial carcinoma masquerading as a thin-walled cyst is described by Peabody,

Rupnik & Hanner (48). By no means a common expression of bronchial neoplasm, similar experiences have been encountered by other radiologists. Congenital cystic pulmonary malformations in infants have been presented by Craig, Kirkpatrick & Neuhauser (49). The appearance and the ultimately proved identity of various mediastinal tumors in children provides a basis for discussion by Singleton & Biles (50).

Chicken pox pneumonia, a disease scarcely to be expected frequently in one's daily practice, has received particular attention during the year [Tan, Kaufman & Levene (51); Southard (52)]. Profound and undesirable complications of cardiospasm in the form of lipoid pneumonia and cor pulmonale are reported by Steinberg & Finby (53). Less spectacular examples of aspiration pneumonia are common-place in the experience of all radiologists. In describing and reporting an example of chronic melioidosis, Oderr & Shaw (54) demonstrate the similarity of roentgen findings with those to be expected in tuberculosis and offer the opinion that *Malleomyces pseudomallei,* an organism resembling that of glanders, may be more common in humans than published examples might indicate. Sarcoidosis, a perennial source of speculation and interest among those concerned with pulmonary diseases, can be the responsible factor in the production of middle lobe syndrome [Arkless & Chodoff (55)], and histoplasmosis can be encountered as an acute fulminating pulmonary disease [Fissel (56)]. The bizarre and sometimes inscrutable alterations in the appearance of the chest produced by total collapse of one lung are described and clarified [Lubert & Krause (57)]. Not until the past 10 years has the propensity of histoplasmosis to produce calcium deposition in lung and mediastinal lymph nodes been fully appreciated. The subject is discussed and well-illustrated by Serviansky & Schwarz (58). The widespread interest in the early detection of primary neoplasms of lung has led to a great deal of observation and discussion on the part of radiologists seeking to find highly reliable methods of differentiating between neoplastic and inflammatory lesions which can so closely resemble each other. The reliability of assuming that calcification within solitary pulmonary nodules eliminates the likelihood of primary neoplasm is carefully and expertly analyzed by O'Keefe, Good & McDonald (59), while Bleyer & Marks (60) discuss the radiologic differences between tuberculoma and hamartoma as they occur in the lung.

A most uncommon pulmonary situation, presented so masterfully in exhibit form as to receive the gold medal of the Radiological Society of North America, is to be found in pulmonary alveolar microlithiasis which appears to occur in multiple individuals within families [Sosman *et al.* (61)]. Hemosiderosis, repeatedly the subject of discussion in current literature for the past several years, is comprehensively discussed by Bruwer, Kennedy & Edwards (62).

Each year there seem to appear from nowhere newly recognized diseases, or at least previously undescribed radiologic manifestations of diseases,

which attract the attention and the interest of radiologists. This year in the field of pulmonary radiology nitrogen dioxide pneumonia, or silage gas poisoning, found among agricultural workers, is presented by Grayson (63).

THE CARDIOVASCULAR SYSTEM

The recent surge of new techniques which have expanded vastly the potential of radiology in this important field of medicine is all the more startling and important when examined against the backdrop of everything that has gone before in cardiovascular roentgenology. It is for this reason that the review article by Fulton (64) is included here. Even with the advent of new, elaborate, and complicated procedures it is pointed out by Bruwer (65) that the simple posteroanterior projection of the chest, coupled with fluoroscopy, can be most helpful in the analysis of certain types of heart disease. On the other hand, Figley (66) points out that cardiovascular radiology is expanding its horizons at a rapid rate and typical examples of the ground gained thus far are presented. The close interrelationship between the new diagnostic methods in the hands of the radiologists and present accomplishments and future possibilities in the field of cardiovascular surgery are discussed by Bahnson (67).

A simple, workable, and dependable method for the study of lower extremity vessels in the case of suspected arteriosclerosis obliterans is presented by Rogoff (68).

The subject of splenoportography which, during the past year has come into its own in a very large measure, is presented here through reference to an excellent article by Evans & O'Sullivan (69). A most interesting and unexpected situation, infantile arteriosclerosis, deserves consideration [Weens & Marin (70)], while Hilbish & Cooley (71) call attention to the fact that congenital mitral stenosis can and does occur. Over and beyond the extensive and intriguing field of congenital cardiovascular malformations which can be studied to advantage with the newer angiographic techniques, the urge to detect and evaluate acquired valvular lesions in man has led to a direct attack upon the chambers of the left heart in order that the function of the mitral valve, so commonly involved in acquired heart disease, may be studied profitably and accurately. The subject is well presented this year by Lehman, Musser & Lykens (72). It is one thing actually to observe opaque material entering parts of the heart and its great vessels through abnormal orifices, and another, by a more adroit method of observation, to detect dilution of such opaque materials by nonopaque blood escaping through similar defects to mix with the opaque material and dilute it. This subject is presented and discussed well by Figley *et al* (73). Among the pioneers of angiocardiography, Lind, Rocha & Wegelius (74) indicate to what advantage fast angiocardiography can be helpful in arriving at an early diagnosis of patent ductus arteriosus. Buenger, Paul & Fell (75) report a calcified polyp within the heart, discovered by them as a most unusual and intriguing finding.

The use of iodine-containing materials to impart recognizable contrast to circulating blood has long been the subject of considerable investigation and concern. An elaborate physiologic investigation of the biologic effects of such materials as used in angiocardiography is offered by Rowe *et al.* (76), while demonstrable injury to the spinal cord resulting from contrast material used in aortography is reported by Margolis, Tarazi & Grimson (77).

GASTROINTESTINAL TRACT

Abnormalities involving the lowermost portion of the esophagus, the upper portion of the stomach and, in particular the esophago-gastric junction, are a constant source of interest to all radiologists engaged in this form of work. Each year suggestions for the improvement of diagnostic accuracy in this connection are offered. This year new hints regarding the diagnosis of esophageal varices, the particular features of hiatus hernia occurring in pregnancy, and an analysis of 453 examinations with respect to reflux into the esophagus have been presented [Nelson (78); Mixson & Woloshin (79); Conway-Hughes (80)].

Davis & Adams (81) call attention to some of the roentgen findings which can be considered quite characteristic of gastric leiomyomas and leiomyosarcomas.

The various facets of radiologic and clinical interest in the field of gastric ulceration have received extensive attention as usual in current radiologic literature. The subject is well-reviewed by Elliott, Wald & Benz (82), while particular emphasis upon the radiologic aspects of gastric ulcer in other people is presented by Klein & Bradley (83). The overworked statement that gastric ulcers occurring on the greater curvature are malignant more often than not is once again disproved by Feist & Littleton (84), and the early manifestations of malignancy related to gastric ulceration are outlined by Lloyd (85). Sloan (86) has presented the results of a most interesting anatomic study of the pattern of the mucosa throughout the small intestine, a subject which has not received the continuing study it deserves. The strange disease "regional enteritis" is by no means limited to the terminal small bowel and, once again its occurrence high in the intestinal tract, this time the duodenum, is reported by Keats & Brady (87). No annual review of diagnostic radiology would be complete without some reference to Meckel's diverticulum which every diagnostic radiologist secretly hopes one day to discover by x-ray means before operation. Mehta (88) has achieved this distinction. The limbo of poorly understood abnormalities which can affect the form and the behavior of the small intestine contains many unusual underlying disease situations. Intriere & Brown (89) call attention to one of the little-known situations which can produce such findings—primary amyloidosis, and another reference to the same situation is provided by Korelitz & Spindell (90). Ramos & Powers (91) offer a well-documented example of a most unusual and uncommon situation—pneumatosis cystoides intestinalis.

Even the most experienced radiologist might well be trapped into reporting radiologic signs of bowel obstruction by the striking appearance of fluid levels in multiple diverticula throughout the small intestine reported by Strömme (92). Robinson (93) calls attention to the great difficulty of achieving completeness and high levels of accuracy in the search for polypoid lesions throughout the colon. This is a subject which deserves the full attention of gastrointestinal radiologists because of the great frequency of the lesions and their serious importance if allowed to go unrecognized. McBurney & Sanders (94) discuss the familial type of polyposis which we believe always leads to malignant neoplasia if allowed to remain. In apparent contradiction, certain polyps of the colon as they occur in children have been shown to regress spontaneously by Andren & Frieberg (95). This section on gastrointestinal radiology would not be complete without inclusion of a reported fatality following the very commonly employed procedure of barium enema [Peterson & Cayler (96)].

BILIARY TRACT

In recent years there has been a very considerable literature related to radiologic methods of examination of the gallbladder, the biliary ducts, the spleen, and the splenic and portal veins. Much of the interest has centered around newly introduced opaque materials for oral and intravenous administration, the most recent being Sodium iodipamide (Cholografin) for intravenous demonstration of the biliary duct system in particular. This can be accomplished even after removal of the gallbladder in a considerable proportion of patients. A hundred clinical trials for the purpose of seeing both the gallbladder and the biliary ducts are reported by Shehadi (97). For a more complete review of the entire subject of cholecystography and cholangiography, one should consult Aldridge (98).

Excellent radiologic technique, important in all phases of roentgen diagnosis, is particularly imperative if the choicest fruits of this type of examination are to be harvested. Hoffman (99) has found that phototimed spot films under fluoroscopic control with the patient in the upright position provide an extremely high order of technical excellence in cholecystographic filming. The often repeated legend of gallbladder regeneration following surgical removal is carefully discussed by Frommhold (100) who comes to the conclusion that the belief is, in fact, nothing more than a legend. Some neoplasms which metastasize to the liver are capable of laying down lime salts and this interesting subject is nicely documented by Wells (101). An example of total calcification of the spleen is presented by Jünemann (102).

Since the days when thorium dioxide (Thorotrast) in very large doses was employed to produce opacification of the liver and spleen, the search for other useful agents which do not carry the very great disadvantage of radioactivity has gone steadily forward. Ethyl diiodostearate (Angiopac) is one of the most recent materials to be suggested. Berger (103) finds that its toxic side effects are, in all probability, sufficiently important to prevent

its use clinically, even though there are some interesting possibilities to be observed. On the other hand, a new hepatolienographic agent, tin oxide, would seem to have the great advantage of long-proved tolerance by the human body, for tin miners with spectacular stannicosis are known to have lived for many years with no demonstrable ill effects from the tin. Fischer (104) uses this as a strong argument in favor of the newly suggested employment of tin oxide. Culver & Pirson (105) have interesting comments and observations to offer regarding aneurysms involving the splenic artery. According to them, aneurysm is associated very commonly with demonstrable calcification of the splenic artery and the situation is, in all probability, less uncommon than radiologists were wont to think in the past.

In Sweden great interest has been shown in the recent past in the subject of lymphadenography whereby lymph nodes representing drainage areas from the sites of primary neoplasms can be rendered opaque by material injected intravenously at or near the primary site. This interesting subject is presented by Brunn & Engeset (106).

Very shortly after the reported results of the intravenous injection of thorium dioxide for opacification of liver and spleen made their appearance, serious doubts were expressed by many that the method could survive because of the dangerous side effects to be expected from the use of a radioactive opaque material. Within this past year still another well-documented example of biliary tract neoplasm following this heroic procedure is reported by Roberts & Carlson (107). In this particular instance the neoplasm was an hepatic duct carcinoma discovered 17 years after thorium injection.

GENITOURINARY TRACT

In the course of its clinically important application throughout the past year, urologic radiology has not produced much in the way of outstanding new developments or new observations. Only a few of the papers on genitourinary matters seem to have emerged as subjects of new and lasting interest. A peculiar and striking increase in the density of bone within the ilia immediately adjacent to the sacroiliac joint has been studied by Wells (108) who finds that the situation occurs predominantly in women (80 per cent) who have previously gone through pregnancy. As far as she has been able to determine, the situation, arresting as it is in roentgenograms, carries no clinical importance. A demonstration of a valuable dividend to be derived from soft tissue filming of the pregnant uterus shortly before the beginning of labor is presented by Engle, Jacobson & Fraser (109). They were able to show quite convincingly that prior to delivery the existence of bicornuate uterus can be foretold with accuracy, often to the great advantage of the patient.

The investigation of patients with heterosexual development can be enormously aided by the use of radiologic examination methods. Important evidence leading to the correct identification of predominant sex is demonstrated in numerous instances by Tristan, Eberlein & Hope (110). Patients of this type who, to be sure, are not encountered in great numbers, require

the greatest ingenuity which can be focused upon the subject if important decisions regarding the determination of sex are to be forthcoming.

Despite the great achievements over the past 60 years which might seem to have exhausted the potentialities for exploitation in the field of diagnostic radiology, the growth of this clinical specialty continues at an ever increasing tempo. There is little reason to believe that widespread fear of immediate or future biologic damage resulting from the clinical application of radiations will prevent their continued use where the associated benefits are so clearly apparent, and the considerable further development of diagnostic techniques of great promise. Certainly it is the responsibility of radiologists and all consultants with whom they work to weigh, in every instance, the beneficial results to be expected from diagnostic procedures involving the use of x-rays or other sources of radiation against possible dangers, however slight or remote. The general public has a distinct right to expect this consideration of its best interests by its physicians, and there is no doubt that this expectation will be realized.

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TOXICOLOGY OF RADIOACTIVE MATERIALS[1,2]

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Of the thousand or so radioactive nuclides (1) that have been discovered or identified, there are actually only about twenty that are produced or used, or both, in sufficiently large quantities or have sufficiently long half-lives to constitute potential health hazards. In general, these are naturally-occurring, nuclear pile-produced, or result from fallout. A listing of these, together with a compilation of significant data for evaluating their potential toxicity, are presented in Table I.

This table is adapted from tables given in the Recommendations of the International Commission on Radiological Protection (2) and the National Bureau of Standards Handbook 52 (3). The particular nuclides which were selected for listing and discussion are those: (*a*) which, on entry into the body, remain there for a long period and continuously irradiate selected organs. These nuclides, in general, localize in the skeleton and are toxic in extremely minute quantities; (*b*) which are not as toxic as the bone seekers but are used in large quantities, as judged from the distribution statistics of the Oak Ridge National Laboratory (4, 5), and hence have a high probability of exposure to a significant number of people; and (*c*) which are persistent fallout products and present a long-term, low-level hazard to the population in general. The data contained in Table I are taken directly from the tables indicated above unless otherwise indicated. The original sources of the data can be obtained by referring to these tables. The data apply only to soluble inorganic forms of the nuclides unless otherwise indicated.

In a general sense, a radiation source produces the same effect on cells whether it is within the body or irradiating it from the outside, i.e., it produces ion pairs which, in some as yet unknown fashion, disrupt nucleoproteins or alter enzyme systems. However, for an adequate evaluation and understanding of the toxicity of a specific radioactive nuclide with the accumulation of the same type of information as is necessary for the toxicology of the so-called conventional poisons, the chemical toxins, is required. For instance, in both cases it is desirable to know (*a*) the form of the material, i.e., whether soluble or insoluble; (*b*) the route of entry; (*c*) the extent of absorption across the gastrointestinal tract; (*d*) the amount absorbed through the lung alveoli; (*e*) the rate of resorption from an intramuscular or subcutaneous site; (*f*) the routes and rate of elimination;

[1] The survey of the literature pertaining to this review was concluded in June, 1957.

[2] The following abbreviations are used: MPD (maximum permissible dose; CaEDTA (calcium ethylenediaminetetraacetate); BAL (2,3-dimercaptopropanol); RBE (relative biological effect); HTO (hydrogen-tritium oxide).

TABLE I

DATA OF INTEREST FOR ESTIMATION OF THE HAZARD FROM RADIOELEMENTS

Nuclide	Mode of Decay	Retention (Half-Life in Days)			Accumulation in Principal Organs of Retention (Per cent)	Per Cent Absorbed from GI Tract	Per Cent from Lung to Principal Organ of Retention	Maximum Permissible Dose in μc
		Physical	Biological	Effective				
H^3	β	4.6×10^3	10	10	100 (whole body)	100	75	3.7×10^3
C^{14}	β	2.09×10^6	varies with the compound in which it is incorporated					250
Na^{24}	β, γ	0.62	29	0.61	100 (whole body)	95	73	5
P^{32}	β	14.3	1200	14	90 (lymphoid tissue, bone)	70	20	10
S^{35}	β	87.1	varies with the compound in which it is incorporated					100
K^{42}	β, γ	0.52	33	0.51	75 (muscle mass)	90	53	20
Ca^{45}	β	164	7.3×10^4	164	99 (bone)	40	40	15
Co^{60}	β, γ	1.89×10^3	8.4	8.4	68 (liver)	20	>1	3
Sr^{90}-Y^{90}	β	1.02×10^4	7.3×10^4	8.5×10^3	73 (bone)	20	20	1
I^{131}	β, γ	8	138	7.6	20 (thyroid)	100	15	0.3
Cs^{137}	β	1.2×10^4	111*	110	80 (muscle mass)	100	36	90
Ba^{140}	β, γ	12.8	65	10.7	65 (bone)	10	0.2	5
Tm^{170}	β, γ	129	110	59	92 (bone)	.001	6	5
Ir^{192}	β, γ	70	23	17	15 (kidney)	20	2	3.4
Au^{198}	β, γ	2.6	50	26	6 (kidney)	10	7	10
Po^{210}	α	138	20†	48	6 (spleen)	6	1.1	.04
$Ra^{226} + \frac{1}{2}$ daughters	α	5.9×10^5	1.6×10^4	1.6×10^4	99 (bone)	20	26	0.1
Th^{232}‡	α	1.39×10^{10}	7×10^4	7×10^4	73 (liver)	?	?	?
U^{238}	α	1.64×10^{12}	30	30	6.5 (kidney)	.05	.08	0.2
Pu^{239}	α	8.8×10^6	4.3×10^4	4.3×10^4	70 (bone)	.0001	20	.04
Am^{241}	α	1.79×10^5	890	890	90 (bone)	.005	6	.05

* See Reference (130). † See Reference (84). ‡ See Reference (68).

(*g*) the distribution in the body with time and specific organs of localization; (*h*) the pathologic effects; (*i*) the symptomatology; and (*j*) methods of treatment. In addition, for the further characterization of the hazard from a radioactive material, one must know the rate of decay, the mode of decay, and the energy of the emanation. The rate of decay is indicated by the physical half-life in days in Table I. The physical half-life, together with the rate of elimination (indicated by the biological half-life), result in a net loss of the activity from the body, indicated as "effective half-life." The effective half-life T_e can be calculated from the following relationship:

$$T_e = \frac{T_p T_b}{T_p + T_b} \qquad (6)$$

where T_p and T_b are physical and biological half-lives, respectively. The mode of decay, whether by alpha, beta, or gamma emanation, determines the range over which the energy of decay is dissipated. The data on energy of decay, together with the mode of decay and information on the uniformity of distribution of the nuclide in the tissue, are necessary for the calculation of the radiation dose delivered.

A useful index of the toxicity of a radioactive material is the so-called maximum permissible dose (MPD). The more toxic a nuclide, the lower is the MPD. As defined by Stone (*7*), the MPD is the amount of isotope which provides "a dose of ionizing radiation that in the light of present knowledge is not expected to cause appreciable bodily injury to a person at any time during his lifetime." "Appreciable bodily injury" is defined as "any bodily injury or effect that a person would regard as being objectionable or which competent medical authorities would regard as being deleterious to the health and well-being of the individual." The MPD is calculated to be the amount of nuclide that will deliver 0.3 rep per week to the "critical" organ, i.e., the organ likely to receive the most damage, either because the isotope is concentrated in the organ or because the organ is especially radiosensitive. The MPD for "bone seekers" is tied to radium. It is the quantity of nuclide that delivers a radiation dose equivalent to the dose delivered by 0.1 μg. of radium to the skeleton. The MPD is a more desirable index of toxicity than LD_{50}, because it provides a standard against which to judge the continuance of a worker on a specific task. Excellent discussions of the concept of MPD are given by Stone (*7*, *8*), Morgan (*9*, *10*), Taylor (*11*), Jasinki (*12*), Thompson (*13*), and Stannard (*14*).

As can be seen from the topic headings, many of the data indicated above for evaluating the hazard from given nuclides are presented in Table I. Following is a discussion summarizing additional information on certain of the nuclides. In 1953, a comprehensive bibliography was published which abstracted the literature on the toxicology of internally-deposited radioelements through 1951 (*15*). The following review will be devoted largely to reports occurring since that time, although some reference will be made to the earlier literature when it is pertinent to do so. In 1955, a preponderance of work in the field of radionuclides was summarized at the International

Conference for Peaceful Uses of Atomic Energy at Geneva. Since many of the reports were either review articles or contained extensive bibliographies, or both, reference was made to these, when possible.

The Bone Seekers

Radium^{226}.—Radium^{226} and its congeners are the prototypes of the radioactive poisons. The first cases of radioactive poisoning which were recognized and described were radium and mesothorium cases (16, 17). Since that time (1924), hundreds of people have, in various ways, by intent as part of supposed therapy or inadvertently from occupational exposure, accumulated body burdens of radium (18). Many of the cases were well-studied and a considerable body of literature on radium poisoning has been built up (19, 20).

In recent times, because of the atomic energy program, there has been a renewal of interest in these cases since they are a rich and essentially the only source of information on the long-term effects of radioactive poisoning in man. In 1952, Aub *et al.* (21) reported on a series of 30 cases who had stored internally-deposited radioactivity over many years. As might have been expected from earlier studies, the principal findings were in the skeleton, i.e., bone destruction (particularly in the jawbone), "radiation osteitis," pathological fractures, osteosarcomas, fibrosarcoma of a joint capsule. There were three cases of epidermoid carcinoma of the nasopharynx. Three cases with body burdens of 10 to 23 μg. stored as long as 25 years showed no apparent deleterious effects at the time of the study. The lowest dose at which atypical signs were evident was 0.3 to 0.5 μg. These were roentgenographic changes. Marshak (22) reports a similar finding in a case with a body burden of 0.4 μg.

Probably the most comprehensive study on radium poisoning is reported by Looney and his co-workers (23, 24, 25). Among the objectives of this study was the gathering of information on the so-called "minimal bone lesion." Lesions which possibly might be attributed to radium radiation were found in individuals with body burdens of 0.15 μg. in one case, and 0.06 μg. in two other cases. On the basis of his studies, particularly on the microscopic studies, Looney (26) has concluded that the MPD for radium should be lowered from 0.1 to 0.05 μg. and perhaps as low as 0.02 μg., if the dose is accumulated very early in life.

Studies on the early urinary excretion of radium in man were reported by Rajewsky (27) and on the late (i.e., long after the radium had been administered) urinary excretion by Norris and his colleagues (28, 29). Norris points out that the urinary excretion of radium is best described by a power function. Spiers (30) presents a discussion on the radiation dose delivered by radium. An excellent review on the carcinogenic action of radium has been compiled by Furth & Tullis (31).

Plutonium^{239}.—Plutonium^{239} is produced on a large scale. It is used in weapons and as a fuel for nuclear piles. With the vast projected use of

nuclear piles for electric power and for power plants for ships, plutonium will probably become a very important industrial hazard. It is also a component of "fallout." As can be seen from Table I, Pu^{239} has a long half-life, goes to bone on entry into the body and stays there for the remainder of the lifetime of the individual. Because it continuously irradiates a particularly radiosensitive area of the body, the bone marrow, an exceedingly minute quantity of plutonium can be very damaging. For this reason, plutonium has been considered among the most toxic substances known.

The pathological effects on bone are similar to those of radium and the other radioactive bone seekers. The most intensive studies on the toxicity of plutonium in large animals are now being carried out at the AEC Project in the Radiobiology Laboratory at the University of Utah (32). Dogs were injected with Pu^{239} at five different dose levels and are being followed throughout their lifetimes. To date (approximately four years after the start of the experiment) a number of the high-dose dogs have died. The pathological findings are trabecular fibrosis, abnormal endosteal bone growth, pathological fractures, atypical osseous tissues, and osteogenic sarcoma. The clinical findings in the surviving dogs are evidences of premature aging, graying of hair, depigmentation of the iris, retinal changes, and reduced blood volume.

Although Pu^{239} is considered primarily a bone seeker, it has been found to be a potent carcinogen in soft tissues as well as in bone. In an RBE study using development of malignant bone tumors as an endpoint, Finkel (33, 34) found the relative carcinogenic potential for plutonium to be 7:1, as compared to radium. Lisco *et al.* (35) report the induction of fibrosarcoma at the site of a subcutaneous injection in rats of as little as 1 μg. of $Pu(N_3)_4$. In studies done by Wager (36), 1 μg. of colloidal plutonium oxide introduced in the mouse lung resulted in epidermoid carcinoma after one year.

A very sensitive but complicated procedure for the determination of plutonium in urine has been developed by Schwendiman *et al.* (37). The quantitative estimation of the body burden of plutonium is made from the use of curves or equations or both which have been worked out for the correlation of excretion rate and body burden in man (38, 39). The extreme sensitivity of the assay procedures allows for the detection in urine of amounts of plutonium corresponding to very low body accumulations. As a consequence, it has been possible to show that an appreciable number of individuals have accumulated plutonium internally. Cipriani (40) reports that in the Chalk River operations in the year 1953-1954, 10 per cent of the individuals checked for plutonium by urine assay showed accumulation internally. Parker (41) reports that in ten years of operations with plutonium at the Hanford Works, over 100 individuals accumulated plutonium internally. There was no specific exposure incident associated with 45 per cent of these. At Los Alamos, in a report covering six years of operations with plutonium, Hempelmann (42) indicates that 27 individuals accum-

ulated body burdens of plutonium. A similar report from the English experience with plutonium has appeared (43). It is of interest that the preponderance of the cases occurred as a result of inhalation exposure. Also, it is noteworthy that none of these cases accumulated body burdens larger than the so-called tolerance levels, with the exception of one British case (43) and possibly five of the Los Alamos cases (42).

Successful attempts at therapy of plutonium poisoning, namely procedures for hastening the excretion of the metal ion, have been reported in animals (44 to 53). Because of the limited case material, very little experience has been obtained in humans. Foreman presented one case (54) in which the use of calcium ethylenediaminetetraacetate (Ca EDTA) brought about a 25 per cent reduction in the body burden over what might have been expected in the untreated situation. In another case, the drug had very little effect (55). Zirconium citrate, another drug which was found to be very effective in reducing the body burden of plutonium in animals, was tried with little success in humans (56, 57). Graham reports very serious, deleterious side effects from the use of the drug, namely a toxic labyrinthitis (58).

A review of plutonium metabolism covering the literature up to 1951 was published by Katz (59). A meeting on the Therapy of Radioelement Poisoning is reported by Rosenthal (60), and a review on the same subject has been prepared by Schubert (61).

Americium^{241}.—Americium^{241} is an isotope of one of the synthetic transuranic elements (62). It is formed as a by-product in plutonium manufacture and is used primarily in research. Like Pu^{239}, it is one of the most toxic materials known to man. The metabolism and toxicity of Am^{241} are very similar to those of Pu^{239} (63, 64). Although americium is available and used in only small quantities, two cases of internal contamination have been reported. In one case (65), an initial dose equivalent to one MPD was received by inhalation. In the other case (66), a dose of about 27 MPD's was received through a puncture wound in the hand. In both cases therapy was quite successful. In the first instance, the prompt use of Ca EDTA brought the body burden down to a level where americium could no longer be detected in the urine one month after the accident. In the second case, the bulk of the activity was removed by surgical excision of the wound site and the body burden further reduced by Ca EDTA administration.

Isotopes of Lesser Toxicity

Thorium^{232}.—Thorium^{232} is of interest because, until recent times, it was the most widely used radioactive material for medical purposes. Its principal use was as a contrast medium for radiography in the form of colloidal ThO_2, known as Thorotrast. A review of the literature on the biological and medical aspects of thorium has been prepared by David (67). Thorotrast is taken up by the reticuloendothelial system, particularly in the liver, spleen, and bone marrow. The radiation effect is seen in the spleen

and along the sites of injection. Anemias, leukemias, vascular changes, liver damage, and malignancies have all been reported following the use of Thorotrast. However, Looney (68), after a careful review of the literature, states, "It is concluded that the clinical effects from Thorotrast administration over the past quarter century have been minimal. . . . Thousands of patients have received Thorotrast and only an extremely small number of cases have been reported in which the clinical abnormality could be specifically attributed to the presence of Thorotrast."

Uranium^{238}.—Uranium^{238} has been the subject of intensive research from a toxicological viewpoint over the past 10 or 12 years. Results of these studies are largely reported in the publications of the Manhattan Project, in The National Nuclear Energy Series (69, 70). It is interesting to find that the net result of these studies has been the conclusion that the hazard from uranium is more from its chemical effects than from its radioactivity. The MPD of uranium (see Table I) has been determined as 0.02 μc. With the very long half-life of U^{238}, this corresponds to 0.030 gm.; which amount is likely to produce chemical effects in the kidney tubules. In the past 10 years, experience in the uranium mines and mills in the United States has borne out the observations from experiments with animals. Several severe exposures, both with soluble and insoluble compounds of uranium, have verified the conclusions that uranium has a low order of toxicity. Many of the nonradioactive heavy metals, such as lead, arsenic, and mercury, would produce very severe, perhaps fatal, injury at the levels of exposure which have been observed to be innocuous for uranium in man (71). Hodge (72) recently summarized the toxicology of uranium.

Polonium^{210}.—Polonium^{210} is potentially a large-scale industrial hazard. There is great interest in reactors employing molten bismuth as a heat transfer medium. This would yield large quantities of Po^{210} as a result of the irradiation of Bi^{209} by neutrons (73). Currently, Po^{210} is widely used in industry for neutron sources, in self-luminous materials and in static eliminators. The metabolism and toxicology of Po^{210} have been intensively studied in animals (74 to 81). Essentially, it distributes through soft tissue, namely the spleen, kidney, and gonads. Hursh (82) reports that 2,3-dimercaptopropanol (BAL) will markedly decrease the toxicity of Po^{210}. In man, BAL was found to have no effect on polonium urinary excretion (83); likewise, Ca EDTA had no effect (84). Three cases have been reported on the internal accumulation of amounts of Po^{210} above MPD (84, 85). All three occurred as a result of explosions of neutron sources. No deleterious effects were observed in any of the cases.

Iodine^{131}.—Iodine^{131} is the most widely used isotope that is administered internally at the present time. The toxicity of I^{131} is manifest in damage to the thyroid (86 to 90). However, in individuals receiving large doses of I^{131} for ablation of the thyroid in hyperthyroidism or in carcinoma of the thyroid, the toxicity can best be considered as the production of undesirable side effects.

Radiation sickness similar to that following whole-body irradiation has been reported in individuals who had received from 29 to 200 mc. of I^{131} (91). The occurrence of leukemias following administration of I^{131} for carcinoma of the thyroid has been reported (92, 93, 94). Seidlin (95) describes two cases out of 14 who had received approximately 1500 μc. of I^{131}, in whom subacute myeloid leukemia developed five years after the administration of the isotope. However, causal relationship between the occurrence of the leukemias and the I^{131} administration was not very clear-cut.

The carcinogenicity of I^{131} has been demonstrated repeatedly in animals. Asling *et al.* (96) demonstrated the frequent occurrence of carcinoma of the breast in rats following large doses of I^{131}. Chaikoff and his co-workers (97, 98) repeatedly have produced carcinoma of the thyroid in Long-Evans rats with I^{131}. Doniach (99) was able to increase the occurrence of adenomas in the thyroids of rats following I^{131} administration. With the combined use of I^{131} and methyl thiouracil and acetylaminofluorene, he was able to produce carcinomas of the thyroid in rats (100). On the other hand, it has not been possible to produce thyroid neoplasms in mice and in other strains of rats (101). Although I^{131} fails to produce carcinoma of the thyroid in mice, it has been possible to produce regularly pituitary tumors with the isotope when given in doses sufficient to destroy the thyroid completely (102). Gorbman (103) believes that ionizing radiation aggravates or synergizes the thyroidectomy in its tumorigenic action on the pituitary gland.

Notwithstanding these findings in animals, there have never been any cases of carcinoma of the thyroid reported as yet in humans following the administration of therapeutic doses of I^{131}. However, it should be emphasized that evaluation of the carcinogenicity of I^{131} in humans must await the passage of considerable time, at least 10 to 20 years.

Carcinoma of the larynx has appeared in three patients (104, 105) who had received therapeutic doses of I^{131} for thyroid ablation. However, in each case, the length of time between the administration of the isotope and the appearance of the carcinoma (six weeks, 11 months, and 12 months, respectively) appeared too short a latent period to indicate that the tumor was associated with irradiation.

Phosphorus^{32}.—Phosphorus^{32} was the first isotope to be used for therapy (106) and with the passage of time is still found useful for the treatment of polycythemia vera, chronic leukemia, and giant follicle lymphoblastoma (107). The toxicity of P^{32} has been extensively studied in animals (108, 109, 110). The effects are similar in a large measure to those from irradiation and the nitrogen mustards. P^{32} is a potent hemopoietic poison, producing aplasia of the bone marrow and hypoplasia of the lymphoid tissues of the body, including the spleen and thymus. In the peripheral blood the radiation effects are manifested by leukopenia, thrombocytopenia, and anemia. The gonads and upper gastrointestinal tract are particularly sensitive to the effect of the isotope. Other tissues, i.e., liver, pancreas, heart, kidney, and brain, are relatively unaffected.

Like many other radiation sources, P^{32} has been found to be carcinogenic when given in large doses. Its leukemogenic potential in mice is similar to that of x-irradiation (111). Koletsky *et al.* (112) have found in rats that at dose levels of about twice the average therapeutic dose for humans, namely 0.25 to 0.50 μc./gm., P^{32} produced osteogenic sarcomas and squamous cell carcinomas in significant numbers of animals. Toxic effects were not seen in rats given doses of P^{32} which are usually used for therapeutic purposes (113). The question of the leukemogenic action of P^{32} in patients receiving the isotope for therapy of polycythemia vera is still an open one (31).

Gold^{198}.—$Gold^{198}$ is used therapeutically as a colloidal suspension for selectively irradiating neoplastic tissue (114, 115). After intravenous injections it is selectively removed from the blood stream by the cells of the reticuloendothelial system. When given in large doses, a toxic effect was seen in the liver in rats (116) and in dogs (117). Upton *et al.* (118) report the development of hepatomas in several strains of mice following intravenous Au^{198} injection. The only untoward side effects appearing when the isotope was used therapeutically were nausea, vomiting, and a minor depression of the white count (114).

Tritium (H^3), *sodium*^{24}, *and potassium*^{42}.—These isotopes have qualitatively the same toxicological properties. On entry into the body, each one essentially gives whole body irradiation when it is introduced as an ion or as HTO in the case of tritium. Because of the short physical half-lives in the cases of Na^{24} and K^{42} and the short biological half-life in the case of tritium, these materials are relatively nontoxic and the MPD's are relatively high. However, in keeping with the recommendation for other isotopes which distribute throughout the body, the National Committee on Radiation Protection recommended in 1956 (119) that the MPD's be lowered by one-third. This change was made to lower the probability of occurrence of genetic changes and leukemia.

The detection of the internal accumulation of H^3 is made by the assay of any body fluids since, by definition, at equilibrium HTO is uniformly distributed throughout the body. Several new procedures are available for the simple and rapid detection of very low levels of HTO (120, 121). An excellent review on the physiology and toxicology of tritium has been reported by Pinson *et al.* (122). An interesting study by Trujillo *et al.* (123) has shown that when tritium gas is inhaled, there is no direct radiation effect on the lung epithelium. The toxic effect of inhaled tritium gas comes about from the conversion of the element to HTO through either an auto-oxidation or biological mechanism and the subsequent radiation from the compound. There have been no cases reported of toxicity from HTO in man. The therapy in such a case, should one occur, would be simply the forcing of fluids to accelerate the turnover of body water (124).

Na^{24} potentially is a large-scale industrial hazard, since a number of the nuclear power plants now being constructed use molten sodium metal as a heat exchanger. Na^{24} is formed by the action of the neutrons from the pile. The detection and quantitative estimation of Na^{24} and K^{42} in man are simple

procedures, i.e., either by counting the gamma radiation in a whole-body counter (125) or by assay of the activity in the urine. No cases of serious toxicity resulting from the ingestion of Na^{24} or K^{42} have as yet been reported.

Carbon^{14} and sulfur^{35}.—Carbon^{14} and sulfur^{35} are the most useful of the isotopes for tracer studies because these isotopes can be incorporated into a large variety of compounds. The hazard from these isotopes depends largely on the compound of which it is a part.

Other isotopes used in large quantities.—It is fortunate that the isotopes which are used in the greatest quantities present a relatively small toxicological hazard. These isotopes, Co^{60}, Cs^{137}, Ir^{192}, and Tm^{170}, are used largely as radiation sources for teletherapy and radiography and hence are shipped and used encased in heavy metal containers. Consequently, there is very little probability of any of these materials gaining entrance into the bodies of individuals working with them.

Isotopes in Fallout

The testing of nuclear devices by the various powers in the world is resulting in the dissemination into the atmosphere of an amount of radioactive material many orders of magnitude greater than all of the radioactive isotopes that have been produced and used in a controlled fashion (126, 127, 128). Fortunately, the vast preponderance of this radioactivity is short-lived, and because of the mode of dissemination is eventually distributed very widely over the earth. With the tremendous dilution and attenuation, the hazard from this material in a relatively short time becomes one of low-level toxicity of certain of the long-lived fission products. Table II (129) lists the long-lived isotopes found in fallout. Of these, Sr^{90} presents the greatest potential hazard by far, since not only is it a long-lived isotope and produced in relatively great abundance in fission, but it also is readily absorbed from the gastrointestinal tract and locates in the skeleton to re-

TABLE II
Long-Lived Isotopes in "Fallout"

Isotope	Fission Abundance (Per cent)	Half-Life	Per Cent Absorbed	MPD (μc.)
Pu^{239}	—	24,000 years	3×10^{-3}	0.04
Cs^{137}	6.2	33 years	100	98
Sr^{90}-Y^{90}	5.1	28 years	35	1
Pm^{147}	2.6	3.7 years	3×10^{-2}	25
Ru^{106}-Rh^{106}	0.5	1.0 year	5×10^{-2}	4
Ce^{144}-Pr^{144}	5.3	275 days	3×10^{-2}	1

main there for a long period of time. Cesium^{137} is also formed in approximately the same abundance as Sr^{90} and has an even longer half-life, but its metabolic characteristics, namely, wide distribution throughout the body muscle mass and relatively rapid turnover [approximately 140 days in man (130)], render it far less hazardous than Sr^{90}.

Much of the Sr^{90} which was formed in fission now lies scattered in the upper two inches of soil in an irregular pattern over the surface of the earth. The remainder is still suspended in fine particles in the stratosphere and is slowly falling out with a half-time of about seven years (131). The levels of Sr^{90} in the soil at various parts of the world are determined by several factors: the proximity to the test sites, the types of devices shot off, and meteorological conditions, particularly rainfall. It is estimated that the highest concentration of Sr^{90} in the soil at the present time (January, 1957) lies in the region of the midwestern United States, i.e., 29 $\mu c./M^2$ (132). In a belt around the world between 60°N-10°N latitude, the concentration in the soil is estimated at 16 $\mu c./M^2$, and over the rest of the world an average of 3.6 $\mu c./M^2$.

The evaluation of the hazard to the population of these quantities of Sr^{90} in the soil, as well as the amount of settling on the foliage of plants, involves the determination or estimation of the amount of Sr^{90} which has or will be accumulated in the skeletons of the population through the food chain, and the estimation of the long-term radiation effects for these amounts in the skeleton. In evaluating the hazard from fallout in general, consideration must be given to the Sr^{90} yet to come down out of the stratosphere as the result of past tests and, of course, to that formed in future testing.

At the present time, it is certain that everyone in the world has accumulated some Sr^{90} in his skeleton, albeit an exceedingly small quantity. Actual measurements are as follows: measurement of Sr^{90} content in the skeletons of stillborns in the United States as estimated by Libby (126) were, on the average, in December, 1953, 0.14 $\mu\mu c.Sr^{90}$/gm. Ca; December, 1954, 0.30 $\mu\mu c.$ Sr^{90}/gm. Ca; and in December, 1955, 0.66 $\mu\mu c.$ Sr^{90}/gm. Ca. Kulp *et al.* (133) report Sr^{90} analyses on 484 samples of human bone collected during 1955 and early 1956 from 17 stations distributed throughout the world. The average Sr^{90} concentration for all ages was 0.12 $\mu\mu c./gm.$ Ca with some values running 10 times as high as this. The bones of children gave values three times this, i.e., the average concentration in 64 bone samples from children from less than one year to four years old was 0.31 $\mu\mu c./gm.$ Ca. Bryant *et al.* (134) report analyses on 28 bone samples collected in England during early 1956. Eight samples from children, three months to three and one-half years of age, averaged 0.9 $\mu\mu c.Sr^{90}$/gm. Ca. In adults, the average was 0.07 $\mu\mu c.$ Sr^{90}/gm. Ca.

Estimates of future levels of Sr^{90} in the skeletons of the population have been made by several competent individuals. The numbers vary greatly depending, of course, on the basic assumptions and the figures used for

calculation. By 1970, Kulp (133) estimates the average level in the population of the United States will be 2 μμc. Sr^{90}/gm. Ca. Langham (129) gives a figure of approximately 3 μμc. Sr^{90}/gm. Ca level in children by 1975. Libby (126) estimates the range between 10 and 40 μμc. Sr^{90}/gm. Ca; Eisenbud (135), 25 μμc. Sr^{90}/gm. Ca; and Jones (136), 50 μμc. Sr^{90}/gm. Ca. The first two figures are based on the assumption that there would be no further testing after 1956. The others assume testing will continue at the present rate. The last two estimates are high, since they are indicative of an upper limit which minimizes the Ca/Sr discrimination factor which has been observed to operate at various levels in the ecological chain involving strontium (137, 138, 139).

The hazard from very low levels of Sr^{90} is very difficult to evaluate since it will be manifest, if at all, years from now in an increase in common pathological phenomena which occur both from other causes and from natural (and unavoidable) radiation, i.e., an increase in neoplastic disease, increased mutations, or shortening of life span. These increases must be judged from careful statistical analysis of vital data from large populations. Predictions of the hazardous nature of Sr^{90} from fallout have been made using various yardsticks. Comparisons have been made between the present and predicted levels in bone and the MPD as indicated in Table I. The MPD for Sr^{90} is 1 μc., which corresponds to 1000 μμc. Sr/gm. Ca. For the population at large, the MPD has been judged to be one-tenth of that for workers using radioactive materials, i.e., 100 μμc. Sr/gm. Ca. Using these criteria, if testing is stopped or is carried out at a rate which maintains the current levels of Sr^{90} in the biosphere (the rate of production of Sr^{90} is kept at the level of Sr^{90} decay), then many of the "experts" (140, 141) feel the hazard is sufficiently small that the benefit of continued testing justifies the risk. On the other hand, there are opinions that the 100 μμc. level is too high a MPD for the general population, particularly for children, and should be 50 (140) or 1 μμc. (142). If this is so, then the population may already be committed to a MPD of Sr^{90}.

Another means of evaluating the Sr^{90} hazard is to compare the dose to the skeleton received from the isotope with the dose from radiation received from everyday living. Dudley (143) estimates that the average natural dose rate to the skeleton is 121 mrem/yr. To this must be added about 70 mrem/yr. from radiations due to x-rays, etc. In 70 years at this dose rate, the integrated dose is approximately 10 rem. The dose from 100 μμc. Sr^{90}/gm. Ca over 70 years is approximately 10 to 20 rads, depending on the method of calculation. If this level of radiation produces appreciable deleterious effects, then not only must we be concerned about fallout but even more so about minimal amounts of radiation which are given for medical purposes.

Lewis (144) has written a provocative article on the induction of leukemia by ionizing radiation. He estimates that the 100 μμc. Sr/gm. Ca-level in the population would increase the present incidence of leukemia by 5 to 10

per cent. His estimations were made from figures extrapolated from data in the range of over 100 r down to doses of from 10 to 20 r and thereby assume that there is a linear relationship between dose and leukemia incidence at all dose levels, an assumption which is highly questionable.

With respect to life span changes for the levels of radiation from Sr^{90}, Jones (136) states, "The effects are dwarfed in comparison with the adverse environmental hygienic factors that most people regard as commonplace," i.e., smoking, overweight, riding in automobiles, etc.

Although it is commonly agreed among geneticists that any amount of radiation, however small, has the probability of inducing a genetic change, and that radiation doses are cumulative in their effect in genetic material, it is of interest to point out Muller's (145) statement to the Congressional Committee, "I must emphasize, too, that I estimate fallout to be at present a negligible hazard to the genes we must pass on to future generations." Crow (146), before the same Committee, stated, "Despite the quantitative uncertainty of these estimates, I believe that they have enough validity to permit some definite conclusions. One is that with the present levels of fallout, the amount of genetic damage in future generations from this cause will be a very small fraction of the total death, disease, and misery. On the other hand, the number of persons exposed to fallout is as large as the world population, and therefore we can be sure that several hundreds, or thousands, or tens of thousands, or perhaps more persons will be diseased, or deformed, or will die prematurely, or be otherwise impaired, as a consequence of fallout, if the present rates of testing continue."

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DISEASES OF THE SKIN[1]

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In this review, which must be arbitrarily selective because of limited space, attention will be centered only on those areas of dermatology which for one reason or another have most attracted current interest, or in which it is felt that recent advances in thought, knowledge, or practice seem to have taken place. Subjects were chosen which were not covered in the last review on dermatology in this *Review* in 1954, or which have developed since then.

Therapy of Skin Diseases

In the area of chemotherapy of dermatologic disorders, isonicotinic acid hydrazide (INH) has clearly emerged as the main weapon used against all varieties of cutaneous tuberculosis (1). Discussions about the advisability of combined use of this drug with other antituberculosis agents such as *para*-aminosalicylic acid, streptomycin, and even calciferol continue (2, 3, 4) although these questions are probably better decided in individualized fashion in the management of the particular case. The importance of prolonged therapy with INH in cutaneous tuberculosis as well as long-term follow-up of such cases is generally recognized.

Since 1940, sulfapyridine has been practically the sole highly effective chemotherapeutic agent used for the long-term suppression of dermatitis herpetiformis. Recently, however, the usefulness of sulfones as an important new class of chemotherapeutic agents against dermatitis herpetiformis has been widely confirmed (4, 5, 6), following their introduction into the therapy of this disease independently by Cornbleet (7) in the United States, and by Esteves & Brandao (8) in Portugal. In some cases therapeutic response has been even superior to that achieved by sulfapyridine. As with sulfapyridine, maintenance doses of the sulfones are necessary for continued suppression of the disease and these doses need to be individualized. At times relatively small doses may be effective as, for example, 50 mg. daily of diamino-diphenyl-sulfone (DDS, Dapsone). Of course, other sulfones such as sulfoxone sodium (Diasone) and acetosulfone (Promacetin) have been similarly effective.

Another class of chemotherapeutic agents, the iodoquinolines such as diiodohydroxyquin (Diodoquin), have also been established as having a new, often great and, indeed, life-saving, specific value in the management of acrodermatitis enteropathica, a recently delineated (9), often fatal syndrome of infancy and childhood (10). Acrodermatitis enteropathica is a rare disease tending to occur in familial fashion and is characterized by

[1] The survey of literature pertaining to this review was concluded in July, 1957.

sprue-like gastrointestinal difficulties, disturbances in growth and development, alopecia, apathy with schizoid behavior, and distinctive circumscribed erythematosquamous to papulobullous patches about body orifices and on distal parts of the extremities. Complicating mucocutaneous candidiasis is a very frequent, almost universal feature of the disorder and accounts for the fact that cases of this disease in the past were often diagnosed as atypical forms of systemic moniliasis. The primary focus of this unusual disease appears to be in the gastrointestinal tract and autopsy findings in a recently reported case support this view (11). On occasion intestinal giardiasis has been associated with the syndrome (12, 13).

In the area of disorders involving melanin pigmentation, the psoralens and monobenzyl ether of hydroquinone have attracted considerable interest despite very important drawbacks to their practical therapeutic use. The very fact that these agents can influence melanin production in the skin is, of course, significant.

The psoralens (furocoumarins) are a class of cutaneous photosensitizing compounds produced in nature by a variety of plants. These natural sources include bergamot and other citrus fruit oils (well-known causes of the hyperpigmentation of berloque dermatitis), parsnips and also the fruit of Egyptian plant, *Ammi majus*. The latter had been used for centuries as a folk remedy for vitiligo. Early investigations of Fahmy & Abu-Shady (14) and by El-Mofty (15) on the active substances produced by this plant led to a wave of interest in the psoralens (16, 17) and to commercial synthetic production chiefly of 8-methoxy-psoralen (8-MOP) for the treatment of vitiligo. This agent, in order to produce its significant cutaneous effects, must be used in conjunction with ultraviolet irradiation preferably from sunlight. Both local and systemic administration have been recommended. Local application has too frequently led to rather unpredictable violent blistering photosensitization reactions and hence has been largely abandoned. Simultaneous use of topical hydrocortisone preparations has not been able to prevent or counter these severe reactions (16). Oral administration of tablets containing the drug followed by exposure to sunlight 2 to 3 hr. later has been the usually advocated procedure in treating vitiligo. Although after many weeks or months of this regimen some degree of repigmentation often occurs, it is generally incomplete so that the cosmetic result is satisfactory in only about 25 per cent of cases. Furthermore, the accentuated melanization of nonvitiliginous areas often unpleasantly increases the contrast between normal and involved skin. Aside from this unpredictable response, a much more serious drawback to this therapy has been the hepatotoxic and nephrotoxic potential of the medication (16). Evidence suggesting liver toxicity during the use of psoralens in vitiligo has, on several occasions, been detected by abnormalities in various flocculation tests of liver function (16, 19). In view of the entirely benign nature of vitiligo and the great uncertainty of therapeutic results, the risk of liver damage from

psoralen therapy can scarcely be accepted, even if the risk is small with the doses recently recommended.

The suggested possible use of 8-MOP on a large scale simply to enhance physiological sun-tanning as has been described in sensational magazine articles directed to laymen is unfortunate (20), although it is of interest that tolerance to sunlight can be increased as a result of such psoralen-induced melanosis (21, 22).

Occupational leukoderma induced by exposure to monobenzyl ether of hydroquinone was described and studied many years ago (23, 24). Recently attempts were made to popularize topical use of this material in ointment form to bleach hypermelanotic conditions such as chloasma (25). The chief drawbacks to this therapy are the high incidence of allergic sensitization to the compound and the inability to predict or control the degree and extent of the resulting leukoderma. Not infrequently, the resulting leukoderma is as objectionable cosmetically as was the original melanosis. Ill-advised attempts to treat such objectionable leukoderma induced by monobenzyl ether of hydroquinone with psoralens have resulted on occasion in a most disfiguring, intensely contrasting leukomelanoderma.

In the management of superficial fungal infections other than those caused by *Candida albicans,* the introduction of glyceryl triacetate (Triacetin) preparations (26) appears to be a significant advance as it eliminates the objectionable odor associated with the use of free fatty acid preparations. Triacetin is applied topically for antifungal effect in concentrations of 25 per cent or higher in alcoholic or carbowax ointment vehicles. Early results in recalcitrant *Trichophyton purpureum* infections seem to be somewhat superior to those achieved by previous methods of therapy. It is believed that lipases in the fungi as well as in serum and on the skin surface hydrolyze the constantly present reservoir of triacetin to release acetic acid in sufficient amounts to effect fungistasis. So far there has been no evidence of irritation or other toxic effect from topical use of this agent and there is no reason to anticipate untoward effects from this simple compound.

Another new antifungal agent which, in preliminary studies shows promise of usefulness in the treatment of superficial mycoses, is butylphenamide, a substituted salicylamide compound (27).

The scarring commonly produced by acne has important psychological and social significance and therefore the popularization of dermabrasive techniques especially for the treatment of such scars cannot be ignored. The history of rotary dermabrasive techniques since their introduction in Germany in 1905 by Kromayer is reviewed in detail by Blau & Rein (28). The major modification in rotary dermabrasive technique introduced by Kurtin in 1952 (29) which led to popularization of the method as an out-patient procedure, was the combination of solid freezing with a refrigerant anesthetic of the area to be abraded with bold application to fairly extensive

surfaces at one session of the motor-powered, rapidly rotating abrasive instrument. Kurtin used specially devised abrasive wire brushes which more recently have been largely superseded by steel burrs (30) which require less frequent replacement and are more readily cleaned. The more hazardous early ethyl chloride refrigerant has also been replaced for the most part by nontoxic, nonexplosive dichlorodifluoromethane (Freon 114), (31). Other technical details of rotary dermabrasion are discussed at length in a thorough monograph on the subject by Burks (32). Complications from the newer dermabrasive techniques have been almost negligible and there is little question of their general safety when performed by operators with the requisite special training and experience. The objective improvement achieved in treating the scars left by acne by this dramatic procedure is at times appreciable, but often fails to match in degree the initial enthusiasm with which it is greeted by the psychologically disturbed victims of such scarring who seek this treatment. It is noteworthy that dermabrasion can safely be carried out even during the active phases of acne and that the procedure has been observed to have a distinctly beneficial effect on suppressing the active disease process. Finally, as reviewed in the Burks monograph, numerous other possible cosmetic applications of dermabrasion are being explored.

The currently fashionable use of almost innumerable tranquilizing drugs has, of course, not spared dermatology. A number of reports have appeared on the adjunctive usefulness of these agents in the management of various pruritic dermatoses as well as skin disorders where psychogenic factors rightly or wrongly were believed implicated such as chronic urticaria, psoriasis, lichen planus, neurotic excoriations, trichotillomania, and palmar hyperhidrosis (33 to 36). It is, however, amply clear from our own experience as well as that of others (37) that these drugs have no specific pharmacologic effect against pruritus associated with diseased skin nor are they specifically beneficial in any of the common dermatoses. In occasional agitated or very anxious patients they may provide some useful tranquilizing effect. From the viewpoint of the dermatologist, the occurrence of cutaneous reactions to these drugs (38 to 44) is of considerable importance.

In the area of topical therapy with anti-inflammatory steroids, a number of effective analogues of hydrocortisone have been tested. Although 9-alpha-fluorohydrocortisone in concentrations of 0.1 to 0.25 per cent has the topical therapeutic effectiveness of corresponding 1.0 to 2.5 per cent hydrocortisone preparations (45, 46, 47), the risk of excessive sodium retention and edema from systemic absorption of this potent compound has generally discouraged its use (48, 49, 50). Topically, 0.5 per cent prednisolone preparations have had an anti-inflammatory efficacy which is only a trifle less than that of 1.0 per cent hydrocortisone (51). Water soluble types of hydrocortisone preparations in 0.5 per cent concentration have been about equally as effective topically as 1.0 per cent hydrocortisone (52).

Concerning absorption of anti-inflammatory steroids through the skin,

studies have shown that 1 to 2 per cent of topically applied hydrocortisone (53, 54) or cortisone acetate (55) is absorbed from normal skin sites and that hydrocortisone penetrates both via transfollicular and transepidermal routes (56). Absorption of hydrocortisone from mucous membrane surfaces is said to range from 26 to 29 per cent (54), and from skin surfaces denuded of their horny barrier layers 78 to 90 per cent absorption occurs within 4 to 6 hr. (57). Obviously, the amounts used in extensive chronic dermatoses should be under the control of a physician. This has been recognized in a recent decision of the Food and Drug Administration of the United States.

Pathogenetic and Clinical Considerations

Along clinical lines, the recently reported successful experimental transmission of the disease, acrodermatitis chronica atrophicans, to normal volunteers by implantation of bits of diseased skin tissue (58, 59), has added convincing support to the already mounting evidence for the infectious nature of this unusual condition. In a recent review of 234 cases of this disease, Hauser (60) points out that, although the skin is chiefly affected by the disease which takes the form of a chronic infiltrative inflammatory process initially and is followed later by profound atrophy, other manifestations also occur. These include nontender regional lymphadenitis with plasma cell proliferation, reactive bone marrow changes, hyperglobulinemia, and increased erythrocyte sedimentation rate. The disease incidence is higher in females than in males and is most often noted in the fifth decade of life beginning in unilateral fashion. It occurs most frequently in rural housewives mainly in Central, Northern, and Eastern Europe. It is less common in France and Southern Europe. It is quite rare in South America and in the United States except among immigrants from endemic areas. The suggestion is made that the disease is an infectious process transmitted by the tick, *Ixodes ricinus,* because acrodermatitis patients give histories of such tick bites and the geographic distributions of endemic areas of acrodermatitis and such ticks essentially coincide. It is suggested further that the higher incidence in rural housewives can possibly be accounted for by their greater exposure to tick bites because of their type of clothing. Several types of antibiotics have been found to cure the infiltrative inflammatory stages of this disease. Foremost among these is penicillin but streptomycin and the tetracyclines have also been effective as has chloramphenicol (61). Clinically, the disease has a disposition to affect relatively cool areas of the skin and exposure to cold seems to favor its progression (60). Tenderness of the periosteum over affected areas to tapping blows is claimed to be a useful clinical diagnostic feature of the disease (59).

In another clinical area increasing attention has been drawn to the rather frequent association of dermatomyositis in adults with internal malignant tumors. Although scattered references to this association had been made for many years (62 to 66), Curtis and his associates (67) in 1952

called attention to the rather high frequency of internal cancer in such patients (more than 17 per cent in their series). They also pointed out that the symptoms of dermatomyositis usually preceded discovery of the neoplasms and that improvement in the dermatomyositis often paralleled the degree of success achieved in therapy of the concomitant neoplastic disease. More recent estimates of the incidence of internal malignant tumors in adult patients with dermatomyositis have ranged as high as 25 to 50 per cent. Thus, in a way similar to acanthosis nigricans, dermatomyositis in adults calls for a most thorough diagnostic exploration to uncover possibly associated internal malignant neoplastic disease.

Gammel recently reviewed the subject of strictly cutaneous manifestations which have been associated with internal cancer (68) and noted, in agreement with Rothman's much earlier review (69), that such manifestations could be generally classified in the following categories: (*a*) pruritus and prurigo-like eruptions with hyperpigmentation; (*b*) toxic bullous eruptions often resembling dermatitis herpetiformis; (*c*) metastatic cutaneous lesions and inflammatory lesions preceding metastases; and (*d*) acanthosis nigricans and similar proliferative changes. To this list he also added figurated urticarial reactions. Still more recently, acquired ichthyotic changes in the skin have been associated on a number of occasions with Hodgkin's or other lymphomatous disease (70, 71, 72).

In connection with a rare type of neoplastic disease, argentaffinoma or metastatic carcinoid, a unique syndrome with prominent cutaneous manifestations has been recognized recently and has attracted much interest (73, 74, 75). This syndrome is characterized by the presence of valvular lesions of the right side of the heart and episodic attacks consisting of very striking cyanotic flushing of the skin especially of the face together with hypotension and a type of respiratory distress resembling bronchial asthma. The paroxysms of cyanotic flushing may also be accompanied by sweating and a feeling of heat. The areas of cutaneous flushing may develop telangiectases and generalized widening of small blood vessels to give a plethoric appearance despite the absence of polycythemia. Gastrointestinal symptoms may often accompany metastatic carcinoid and these include watery diarrhea, abdominal pain, and distress caused by excessive intestinal gas. Palpable metastases may also be found in the liver, and edema, ascites, and pleural effusion may occur. The cardiac difficulties are based upon tricuspid regurgitation or pulmonary valvular stenosis which are believed not to represent congenital deformity but rather to arise from sclerosis or partial fusion of the pulmonary valve cusps. The release of large amounts of serotonin (5-hydroxytryptamine) from the carcinoid tumor is believed to cause the cutaneous and cardiorespiratory manifestations. Analysis of the urine for the excretion of excessive amounts of 5-hydroxyindole acetic acid permits accurate chemical diagnosis of the disorder (76). Sometimes the patients exhibit signs suggesting pellagra and it has been suggested that this may result from diversion of tryptophan metabolism away from normal pathways

of protein and niacin synthesis to production of enormous amounts of serotonin (77).

Varied and ill-defined concepts of what has been called kraurosis vulvae have confused both dermatologists and gynecologists for decades and have resulted in countless, entirely unnecessary, mutilating vulvectomies. Unfortunately, many gynecologic workers still fail to recognize common dermatoses of the vulvar area such as lichenified neurodermatitis, intertrigo, psoriasis, lichen planus, and lichen sclerosus et atrophicus or to differentiate them from premalignant leukoplakia of the area with or without accompanying genital atrophy. A study by Wallace & Whimster (78) based on 100 personally observed cases helps to clarify the difficult and confusing subject of so-called kraurosis vulvae. At the outset these observers recommend that the variously defined term kraurosis be abandoned. They then recognize the following types of vulval atrophy and leukoplakia: (*a*) primary atrophy of the vulva. This relatively infrequent disorder is accompanied by an inflammatory process, is limited in a diffuse way to the vulvar area and is often associated with varying degrees of soreness or local discomfort. Symptoms tend to wax and wane and bland local therapy is suggested as the treatment of choice. These cases need careful observation as there is a strong tendency for the development of premalignant leukoplakia in affected areas. This disorder may occur at any age during adult life but is more frequent after the menopause or when ovarian function becomes defective. (*b*) Senile genital atrophy. A common, usually symptomless, entirely benign, noninflammatory atrophy of the genitalia developing in old age. (*c*) Lichen sclerosus et atrophicus of the vulvae. This is a specific dermatosis with characteristic histologic features. When present on the vulva it is usually associated with perianal involvement. Characteristic lesions consist of ivory-colored, atrophic, lichenoid papules often with follicular hyperkeratosis and plugging. When involvement is extensive there may result severe atrophy of the entire genital area. Pruritus may be severe and the disease may occur even in young children. Signs and symptoms may vary considerably in intensity and spontaneous clearing is especially common in children (79). Bland topical applications are the preferred treatment. Occasionally leukoplakia may develop as a complication and thus periodic examination is necessary. (*d*) Leukoplakia of the vulvae. This is a premalignant, circumscribed hyperkeratinizing process which may follow either primary atrophy or lichen sclerosus et atrophicus or may occur independently of these disorders. Excision or destruction by other means of the leukoplakic areas is indicated after histologic confirmation of activity of the process is obtained.

Knowledge of xanthomatous diseases has been much clarified and advanced by a series of recent studies by Lever and his associates (80 to 88). Initially, they compared the clinical and chemical findings in idiopathic hyperlipemia with those in primary hypercholesteremic xanthomatosis and found that the prime feature which distinguished these two xanthomatous disorders of unknown cause was the striking increase in neutral fat in the

plasma only in idiopathic hyperlipemia. Therefore, simple inspection of the plasma or serum obtained in the fasting state could easily be used to differentiate these two entities because such plasma in idiopathic hyperlipemia is milky in appearance whereas, in primary hypercholesteremic xanthomatosis it is clear. Clinically, the diseases at times may resemble each other because similar cutaneous as well as tendon xanthomas can occur in both. However, eruptive papular xanthomas when present occurred only in the hyperlipemic disease, and xanthelasmata when present were seen only in those of the cases with primary hypercholesteremic xanthomatosis. Prognostically, premature atherosclerotic cardiovascular disease was found to be a hazard in both entities although it occurred with less regularity in idiopathic hyperlipemia. Sharp restriction of dietary fat intake was confirmed to be very beneficial in idiopathic hyperlipemia but of less value in primary hypercholesteremia. Periodic administration of heparin, because of its ability to give rise to the lipemia-clearing factor, was also found useful therapeutically in the hyperlipemic disease and much less so in the primary hypercholesteremic cases. The speed of electrophoretic migration of the serum lipoproteins was also found to be greatly increased in hyperlipemia following the administration of heparin. This was believed to result from binding by alpha and beta lipoproteins of fatty acids released from chylomicra and very high S_f lipoproteins by the lipolytic action of heparin-induced clearing factor. More recently Lever and his co-workers have also reported that intravenous infusions of cottonseed oil emulsions containing soybean phosphatides which produce clearing of plasma in hyperlipemic subjects, act by stimulating the liberation of heparin or a heparin-like substance. The phosphatides alone were found able to accomplish this effect (89, 90). Other evidence, however, suggests that administration of large amounts of unsaturated fat alone even when given orally has a similar lipemia-clearing action (91). Most recently, Klein & Lever (92) report that serum from patients with primary or secondary hyperlipemia inhibits the clearing activity present in normal serum after the intravenous administration of heparin. This observation suggests that the basic defect in these hyperlipemic disorders may be the presence of excessive amounts of an inhibitor of the lipemia-clearing system.

Studies on familial primary systemic amyloidosis have yielded important new knowledge about this rare facet of the amyloid problem. Rukavina, Block & Curtis (93) had the opportunity to investigate 66 members of a family pedigree for this disease by means of clinical, laboratory, and biochemical methods. Evidence for its existence was found in 29 of these individuals and the disorder was clearly inherited as a dominant character. The clinical features which appear regularly in the third or fourth decades consist of peripheral neuropathy, scleroderma-like skin changes, hepatic enlargement and dysfunction, cardiovascular insufficiency, ocular disturbances (floating specks and retinal deposits which may greatly impair vision), gastrointestinal symptoms, splenomegaly, and the so-called carpal tunnel syndrome. Macroglossia, bleeding tendencies, and papulonodular skin lesions

do not occur in this rare familial type of amyloidosis. The usual laboratory procedures were found inadequate for studying these cases. However, studies of serum by free electrophoresis revealed an atypical peak migrating between the beta and alpha-2 globulin areas and ultracentrifugation of the serum showed elevated lipoproteins especially in the −S 25 − 40 and 20 − 25 fractions. These serum abnormalities were adequate to detect subclinical disease.

An entity variously called lichen myxedematosus, scleromyxedema, or perhaps better, lichen fibromucinoidosis has also attracted attention. In this disorder of unknown cause, papular or lichenoid lesions containing much mucinlike material are found in association with diffuse thickening and fibroblastic proliferation in the skin sometimes in bizarre linear distributions (94, 95, 96). There is no demonstrable associated thyroid disease. Abnormal globulins have been implicated in the pathogenesis of this disorder and it is believed that complexes between these serum globulins and mucopolysaccharides of connective tissue origin are deposited as mucinous substances in the skin (97, 98). In a recent case observed by one of the authors, large amounts of an abnormal very slowly migrating globulin were observed on electrophoretic examination of the serum (99).

Another rare disease sometimes marked by papular or linear mucinoid deposits in the skin is gargoylism or Hurler's syndrome (100). In this grotesquely deforming familial disorder which has sometimes been called lipochondrodystrophy there seems to be no abnormality of lipide metabolism but rather widespread deposits of mucinoid material occur in many tissues so that it appears to be fundamentally a disorder of mucopolysaccharide metabolism (101, 102, 103). Large amounts of mucopolysaccharides, especially betaheparin, have recently been found to be excreted in the urine of such patients (104).

A new cutaneous entity which appears to be rapidly increasing in frequency has been described by Weber, Rubin and associates (105) as granulomas of the axillas caused by deodorants. Clinically, this axillary eruption has appeared especially following the use of sodium zirconium lactate deodorant sticks combined with shaving. However, some cases following the use of liquid or cream deodorants not containing zirconium have also been noted. The eruption consists of very chronic, asymptomatic, colorless to dull brownish-red, discrete, translucent, smooth papules one to four millimeters in size. Histologically, dense granulomatous masses with tuberculoid structure are present in the upper corium. Attempts at therapy have so far been unsuccessful. The final outcome in these cases is not entirely clear although the granulomas may apparently disappear spontaneously after several months.

With the advent of extensive use of broad-spectrum antibiotics, a much greater frequency of candidiasis (moniliasis), especially oral and anogenital, has been noted (106 to 109). Fatal cases of systemic monilial infection have also been reported after use of these antibiotics (107, 110 to 113).

C. albicans appears to flourish under such antibiotic therapy not because of any direct growth-stimulating effect on these organisms (114) but rather because of suppression of other flora which normally compete with it. Although the incidence of *C. albicans* in the feces of a given group of people given oral broad-spectrum antibiotics is not increased (114), the numbers of these organisms present in the feces in the individuals harboring it rapidly increase (115). The problem, therefore, appears to be one of activation of quiescent foci in so-called monilia carriers. Other yet unknown factors may also be involved in antibiotic-triggered candidiasis as the claim is made that administration of B vitamins with the antibiotics lessens the incidence of this complication (109). Conjugal transmission of genital moniliasis to males is also occurring with greater frequency with the increased incidence of vulvovaginal moniliasis in women following the use of broad-spectrum antibiotics (116).

A considerable controversy has recently developed over the importance of the contagiousness of superficial mycotic infections of the feet. One group (117 to 120) holds that for practical purposes tinea pedis is not a contagious disease and that public health measures which attempt to prevent its spread are ill-conceived. They feel that exposure to the causative organisms is probably almost universal and that individual and local susceptibility factors are the most important considerations in this disease because of the relative rarity of conjugal infections and the difficulties encountered in trying to establish experimental infections. The other group (121, 122) maintains that even though susceptibility factors are of very great importance in this infection, its contagiosity should not be neglected and that repeated heavy exposures to the infection especially in the family group significantly increase the risk of infection. Recent epidemiological studies in England lend support to this latter view (123).

In regard to the juvenile type of acanthosis nigricans a recent finding of interest has been the association of pituitary basophilism with the disorder without all of the major features of Cushing's syndrome (124). In still another recently reported case, pituitary hypogonadism was found in association with juvenile acanthosis nigricans (125).

Investigative Studies

Along investigative lines there have been numerous advances in dermatologic knowledge. Only a few of these can be discussed here. The work of Shelley & Arthur (126) on the mechanism by which cowhage produces itching has attracted much interest. They extracted a new proteinase, mucunain, from this material which they believe is the active pruritogenic principle. They claim, furthermore, that other endopeptidases with activity in physiologic pH ranges can similarly elicit itching without wheal production when introduced into the epidermis (127). The hypothesis is then suggested that in naturally pruritic skin disorders release of intracellular proteinases (cathepsins) may be a mechanism by which itching is produced.

Confirmation of this attractive hypothesis could have great dermatologic significance as itching is the most important cutaneous symptom and knowledge of its mechanisms is important for the development of badly needed new methods for its control. Some difficulty with this hypothesis has been posed by the failure of trypsin solutions to elicit itching under all conditions in which contact with histamine is most pruritic (128). Objective studies in this field are badly hampered, of course, by the highly subjective nature of the itching sensation.

In the area of endocrine regulation of sebaceous gland function, the demonstration that progesterone as well as testosterone can cause sebaceous glandular hyperplasia in the rat suggests that this hormone is responsible for the development of puberal seborrhea in girls (129). Furthermore, a new sebotropic factor derived from the anterior pituitary gland has been described as being necessary for normal steroid hormone-induced hyperplasia of sebaceous glands to occur in the rat (130, 131, 132). This factor, if present in man, may play a key role in acne vulgaris as well as in the seborrhea accompanying some types of hypothalamic lesions.

In acne vulgaris, the findings that lesions develop only in follicles in the resting phase of the hair cycle and that abnormal excessive follicular keratinization appears earliest only in the special ducts of the sebaceous glands, could have important bearing on understanding of the pathogenesis of this important disorder (133).

The development of the Wolf-Pinkus-Szakall adhesive tape stripping technique by which the horny layers of the skin can be gradually stripped away by repeated application and removal of adhesive tape is proving of great value in many kinds of dermatologic investigations. For example, it has been used to obtain biometric data about the epidermis (134, 135, 136), to facilitate cutaneous capillaroscopy (137), to study histochemical responses to epidermal injury (138), and to investigate the epidermal water-electrolyte barrier (139 to 142) and cutaneous pharmaco-physiology and allergy (128, 143). A motor-driven machine to facilitate the stripping procedure has even been devised (128).

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PEDIATRICS[1]

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Advances in pediatrics since the last *Annual Review of Medicine* have been notable in several respects, of which perhaps three are the most striking: viral infections, enzymatic defects in certain metabolic disorders, and surgical intervention by improved techniques in cardiac malformations regarded until recently as inoperable. Expansion of our knowledge in some other fields has also been noteworthy. Some 21 topics have been selected this year for presentation on which limitations of space have imposed a high degree of brevity. To compensate for this to some extent we offer a fairly comprehensive bibliography.

INFECTIOUS DISORDERS

Bacterial Diseases

Infant diarrhea.—Elucidation of epidemic diarrhea in infancy continues. A detailed review of *Escherichia coli* diarrhea (1) re-emphasized the absence of a unique clinical picture or course, its rapid spread despite rigid isolation technique, and control only after all nursery infants, diarrheal or not, received neomycin. This antibiotic continues to be the drug of choice (2). In a study of *Shigella, Salmonella,* and enteropathogenic *E. coli* recovered in diarrhea by rectal swab cultures, Cooper *et al.* (3), using polyvalent antisera rather than the usual three lots of pooled antisera, found the incidence of enteropathogenic *E. coli* greater than the combined incidence of *Shigella* and *Salmonella.* Their findings suggest that sporadic *E. coli* diarrhea may occur. Zepp & Hodes (4) report a microprecipitin method specific for the B. antigen of enteropathogenic *E. coli* which appears preferable to the colony isolation-slide agglutination method now in general use.

The antibody titer against enteropathogenic *E. coli* rises after the third month of life to a peak in the fourth year. The neonate has a lower titer against *E. coli* 055 and 011 than comparable maternal sera (5).

Skinner & Moll (6) emphasize the frequent occurrence of hypernatremia in infantile diarrhea (25 per cent of their cases in which sodium was measured). These authors state that the mechanism of production of hypernatremia involves profound water depletion or excess sodium administration, or both. They postulate that the kidney in sick infants can clear only 5 to 10 m.eq. of Na/kg. of body weight/day.

[1] The present survey applies mainly to work published between June, 1956 and August, 1957. However, some earlier work has been included dealing with topics of current interest not discussed in previous issues of the *Annual Review of Medicine.*

Childhood tuberculosis.—Debré (7), Robinson (8), and Wallgren (9) agree essentially on the management of primary tuberculosis. The aim is not more rapid regression of roentgen and clinical findings but the prevention of primary progression or of acute generalized postprimary tuberculosis. Infants, adolescents, and those of any age with symptomatic or progressing processes should receive chemotherapy. Isonicotinic acid hydrazide (INH) (10 to 20 mg./kg./d.) for 10 to 12 months with the addition of *para*-amino salicylic acid (PAS), (5 to 10 gm./d.) is suggested. Streptomycin therapy is not advised in primary tuberculosis. Chemotherapy is especially desirable in the three or so months following tuberculin conversion in infancy and adolescence. Further support for specific therapy of primary tuberculosis in infancy comes from Ryder (10) who found no increase in segmental lesions following treatment of mediastinal lymphadenitis. Inadequate initial INH dosage or failure to employ an agent (PAS) inhibiting metabolic inactivation of INH may unfavorably affect chemotherapy (11).

The best therapeutic regimen for tuberculous meningitis is not yet agreed upon. INH as the sole chemotherapeutic agent gave as good results as previous regimens, including intrathecal streptomycin (12, 13). Choremia *et al.* (14) report striking clinical improvement coincident with the intrathecal exhibition of 17-hydroxycorticosterone in tuberculous meningitis but do not claim that it obviates neurological complications.

Citing the possible 80 per cent reduction in incidence of tuberculosis in BCG-vaccinated persons in the report of Medical Research Council of Great Britain, a plea is made for utilizing BCG in infants and children as well as other unavoidably exposed persons (15). Further reports on oral vaccination (16, 17), these employing the BCG-Moreau strain, note a 70-97 per cent conversion to positive tuberculin. Of particular interest is the reported experience with "concurrent vaccinations," (six oral doses at monthly intervals) in which positive reactions become weaker or negative.

As a reminder that all drugs are dangerous, two cases of acute INH poisoning with severe convulsive phenomena are reported (18, 19).

Protozoan Disease

Interstitial pneumonia.—In an extensively documented article, Gajdusek (20) reviews the subject of interstitial plasma cell pneumonia and states the case for a protozoan parasite (pneumocystis carinii) being the etiologic agent.

Viral Infections

In this field, modern techniques and particularly tissue culture, have presented the medical world with an *embarras des richesses* which has culminated in the publication of a symposium under the provocative title of "Viruses in Search of Disease" (21). In this the difficulties in establishing a firm nexus between virus and disease are discussed at length. In the

following section, while presenting such observations as are of particular pediatric interest and as have met at least some of the more important etiological criteria, we must warn the reader that in several instances absolute proof of cause and effect has not yet been established.

Poliomyelitis.—Reported cases of poliomyelitis in the United States have dropped precipitously from the peak of nearly 58,000 in 1952 to half that number in 1955, to about 15,000 in 1956 and, to July, 1957, to about half the corresponding 1956 figures (*22*). While the decline began before the introduction of the Salk vaccine, it has undoubtedly been accelerated by the increasingly widespread adoption of active immunization. The prophylactic effect of the vaccine, as first noted in the Francis report (*23*), is limited to the prevention of paralysis, nonparalytic infection, household and community spread of the virus being uninfluenced by it. This has been shown with particular clarity by the studies of Fox *et al.* (*24*) and Gelfand and his associates (*25*) in Louisiana, who concluded that two doses of the vaccine do not materially reduce the frequency or duration of alimentary infection nor the amount of virus excreted in the feces. The vaccine's effectiveness against paralysis is estimated by the National Foundation for Infantile Paralysis (*26*) at about 75 per cent from two doses, and higher but less than 100 per cent from three. However, Bundesen and his associates (*27*) reporting on the use of the Salk vaccine during the Chicago epidemic in 1956, observed no cases of paralytic poliomyelitis in the estimated 300,000 children who had received three "correctly spaced" injections, whereas the attack rate per 100,000 was 358 for those without vaccine, 154 for those with one dose, and 14 for those with two. Kelly & Dalldorf (*28*) using animal tests, and Shaughnessy and his associates (*29*) studying antibody responses of vaccinated children, demonstrated great variations in the antigenic potencies of different lots of commercial vaccine. The latter authors state that two injections of some lots do not confer adequate immunity. Kendrick & Brown (*30*) using animals, and Batson, Christie & Mazur (*31*) testing infants, showed that three injections of a mixture of Salk vaccine and diphtheria-tetanus-pertussis vaccine (DTP) gives satisfactory antibody response to all four antigens. No hazards or adverse reactions were observed. Attention has been called (*32*) to the lack of evidence that the commonly prescribed 7-month interval between the second and third doses is actually necessary, and that it has serious disadvantages in delaying maximal immunity during epidemic periods. Salk (*33*) has recently reported excellent antibody responses to a third injection given three months after the second. The optimal interval for booster injections has not yet been determined. The latest data indicate that the vaccine has a high but not absolute degree of safety. Langmuir and his associates of the Surveillance Unit (*26*) somewhat guardedly estimate that "the vaccine has influenced the development of considerably less than one paralytic case per million inoculations." Rare allergic reactions but no renal or hematological sequelae have been reported.

Exploration of oral immunization with attenuated living virus continues. The SM and TN strains (Types 1 and 2) introduced by Koprowski and his associates have been investigated independently by Dick *et al.* (34) in Dublin, Ireland. They have found, contrary to previous belief, that after passage through the human intestinal tract, both strains reverted to pathogenicity, causing paralysis after intracerebral inoculation into cynomolgus monkeys. They also observed spread of virus from an inoculated child to other members of a family. These workers believe that the TN and SM strains are not acceptable for mass immunizations but leave the possibility open that suitable strains will be developed, for which they lay down certain minimum safety requirements. In a recent report (35) on his continuing studies of attenuated strains of all three types which he isolated from single plaques, Sabin also observed increased neurotropism by monkey test after excretion of the virus in human stools, but he believes that the danger from human use is minimal since "viruses exhibiting this degree of neurotropism in monkeys are harmless when injected into the spinal cord of chimpanzees." In another place, however, he states that "it would probably require tests on tens or hundreds of thousands of individuals" to establish the absolute safety of the attenuated viruses for the individual and for the community.

Habel & Loomis (36) have identified the Russian "Type 4 poliomyelitis virus," discovered by Chumakov *et al.* (37) in 1956, as Coxsackie A7. The authors call attention to the fact that this strain can actually cause paralysis in monkeys and man and that lesions produced by it in the central nervous system are very similar to if not identical with those produced by poliovirus.

The error and uncertainty in the diagnosis of nonparalytic poliomyelitis, even during epidemics, are forcibly illustrated by the observations of Hammon *et al.* (38) and of Kibrick, Melendez & Enders (39), showing that ECHO 6, as well as certain strains of adenoviruses, can frequently be recovered from patients with aseptic meningitis clinically indistinguishable from nonparalytic polio and sometimes so diagnosed. Further diagnostic confusion is added by the fact that ECHO 6, as well as Coxsackie A7 already mentioned, sometimes causes mild to moderate degrees of muscular weakness, usually transient but sometimes lasting for a considerable period; such cases are difficult if not impossible to distinguish from paralytic polio without thorough virological and immunological study.

Measles.—Enders and his associates (40) state that tissue culture of measles virus has now reached a point where it can be used for measuring the antibody titer of gamma globulin intended for measles prevention, and also for the development of a vaccine. Adams and his associates (41) have demonstrated a close similarity in the bronchopulmonary lesions of human measles and canine distemper, as well as close immunological relations between the two diseases.

Varicella.—Haggerty & Eley (42) report 12 fatal cases of chickenpox

in children being treated for various preceding disorders with cortisone (11-dehydro, 17-OH corticosterone) in doses ranging from 25 to 400 mg. daily, and for a few days to two months before eruption. Among the postmortem findings were hemorrhagic vesicles "throughout all the viscera," and acute encephalitis. Pediatricians should be aware of this danger to patients under cortisone (and probably ACTH) therapy in the face of exposure to varicella. Another and very rare complication of the disease in infancy is hypoglycemia (43), from which all three patients reported died. Thrombocytopenic purpura has also been reported (44); it has a favorable prognosis.

Erythema infectiosum ("fifth disease").—Suggestive evidence has been presented by Werner *et al.* (45) that this acute exanthematous disease, which occurs in widely spaced epidemics, is due to a virus. In studying an epidemic in Reading, Pennsylvania, in 1955, the authors, using tissue cultures, recovered a filterable cytopathogenic agent from nasopharyngeal washings and stools of patients and contacts. Acute and convalescent sera of the latter showed significant rises in complement-fixing antibody against the viral antigens, the controls being negative.

Infectious serum hepatitis.—Beginning with Stokes' report in 1951 (46), a number of cases of acute hepatitis are now on record with clinical manifestations starting in the neonatal period or at a postpartum age less than the upper limit of the incubation period. Probably, therefore, the virus can pass the placental barrier (47, 48). Siblings, including twins (49), have been affected. In some instances, the mother had had acute hepatitis some years previously (50, 51), and in one case maternal hepatitis was recognized during pregnancy (52). It has been suggested that, at a rule, neonatal hepatitis is of the homologous serum (SH) variety, since here the virus persists in the blood stream for long periods whereas, in the IH variety, viremia is limited to the acute prodromal period (46). In the newborn, and in young infants generally, the disease is more severe than at later ages, and is commonly nonicteric (52). Stillbirths and neonatal deaths before jaundice appears have been reported (47) in which typical and severe lesions were present in the liver. Fecal carriage of the virus has been demonstrated (52). A comprehensive study of prevention (53) has recently been published in which, among other things, the hazards of transfusion are stressed.

Adenoviruses (AD, RI, APC, ARD).—First isolated accidentally from human adenoids by Rowe *et al.* (54) in 1953, this important group of viruses, pathogenic for man alone, with a common complement-fixing antigen, is now known to consist of at least 16 serologically distinct types (55, 56). It causes several fairly common clinical syndromes, mainly respiratory, with frequent involvement of the conjunctiva and regional lymph nodes. It is contagious, with a short incubation period of 4 to 5 days, and may occur in epidemics. Types 1, 2, and 3 predominate in children. Clinical forms of pediatric importance include febrile pharyngitis (57), pharyngocon-

junctival fever, epidemic keratoconjunctivitis, laryngotracheobronchitis and bronchiolitis (58). The course of these may be initially stormy, with high fever, but is commonly of rather brief duration. No fatalities have been reported. Recent reviews of the subject may be consulted for further details (56, 58, 59, 60).

ENDOCRINE DISORDERS

Adrenal cortex.—A review of adrenocortical metabolism of the fetus, infant, and child in normal and pathological conditions has appeared during the year (61). This article reviews the knowledge of adrenocortical physiology and pathology up to date and has an extensive bibliography.

Prader (62) has attempted to explain the "salt-losing syndrome" which frequently accompanies congenital adrenal hyperplasia. He has found that aldosterone values in the urine of three infants with congenital adrenal hyperplasia of the "salt-losing" type were normal or slightly increased; in one infant with a healed "salt-losing syndrome" the values for aldosterone excretion were enormously increased; of two adults with congenital adrenal hyperplasia but no history of electrolyte disturbance, one had markedly elevated aldosterone values in the urine, the other had normal values. Prader states that these results prove that the Na loss in congenital adrenal hyperplasia is caused by an as yet unidentified Na-excreting factor. In certain patients the salt-losing syndrome is compensated for a secondary increase of aldosterone production.

Growth.—The effect of testosterone administration on the linear growth of children has been reviewed again by Sobel (63). In a group of 27 healthy, short children five to ten years of age, all doses of methyl testosterone (5 to 40 mg. per day) were equally effective in producing a marked increase in growth rate; however, in two-fifths of the children there was distinctly greater increase in skeletal maturation than in skeletal growth, suggesting that the advantage of an immediate growth spurt may be over-shadowed by a decrease in the ultimate stature, since premature completion of skeletal maturation precludes continued linear growth.

Diabetes mellitus.—A considerable amount of work has been published during the past year related to the effect of certain sulfonamide derivatives on the blood sugar level of both normal and diabetic individuals. These compounds are found to be useful in uncomplicated diabetes mellitus of the stable type in adults, which cannot be adequately controlled by dietary restrictions alone. In the juvenile type of diabetes the sulfonamide derivatives have not proved to be beneficial (64, 65).

Thyroid.—Stanbury (66) has reviewed the subject of congenital cretinism and proposed a classification based on its etiology. It was previously thought that anatomic dysgenesis of the thyroid gland or nutritional factors (iodine deficiency) were the factors involved in the clinical picture of hypothyroidism. Today a new group of conditions clinically similar to athyroid cretinism have been described. These are related to inborn errors

of metabolism with defective synthesis of active thyroid hormones. Most of these cases are familial and have a goiter in addition to signs of hypothyroidism. They often have a normal protein-bound iodine but a very high uptake of radioactive iodine; this is in sharp contrast to the much reduced or often absent uptake in nongoitrous cretins. It is postulated that in these children the increased I^{131} uptake and a significant proportion of the thyroid enlargement are secondary to thyroid-stimulating hormone excess (67). Administration of adequate amounts of thyroid extract produces a suppression of I^{131} uptake and a rapid disappearance of the goiter.

Hazards of cortisone and ACTH therapy.—Good, Vernier & Smith (68) report on the ill-effects of these drugs and their analogues observed in about 10 per cent of their large series. The reactions are grouped as follows: (*a*) disturbances in fluid and electrolyte equilibrium (edema, hypopotassemic shock), 5 cases; (*b*) central nervous system manifestations (status epilepticus, paranoid schizophrenia, hypertensive encephalopathy), 9 cases; (*c*) gastrointestinal disturbances (hemorrhage, perforation), 7 cases; (*d*) infectious disease (staphylococcus infections, pneumonia, cellulitis, herpes zoster), 9 cases; (*e*) skeletal manifestations and miscellaneous complications (pathological fractures, insulin-resistant diabetes, sudden death), 5 cases. Many, but not all, of the above followed heavy or prolonged treatment for severe conditions not amenable to other kinds of therapy. The authors warn that dosages must be kept down to the minimum capable of producing the desired effect. Antibiotics and antacids are routine with large doses. (For another cortisone hazard, see paragraph on varicella.)

METABOLIC DISORDERS

Our understanding of the "inborn errors of metabolism" has been greatly enhanced by recent advances in biochemistry and genetics. We now recognize that an inherited disease may represent a primary abnormality of a single enzyme, the lack or dysfunction of which may result either in the accumulation of metabolites along the involved pathway or in the emergence of altered "adaptive" pathways.

Phenylketonuria.—Phenylketonuria is an excellent example of this concept. Recent reviews by Knox & Hsia (69) and by Armstrong (70) emphasize that the primary defect is a lack of the enzyme necessary to oxidize phenylalanine to tyrosine. Treatment with a low phenylalanine diet results in the return of all biochemical findings to normal and the disappearance of all clinical pathology except mental deficiency. Brain damage is apparently irreversible unless the diet is begun in early infancy (71).

Galactosemia.—The missing enzyme in galactosemia has been identified by Kalckar and his group (72). It is the enzyme which catalyzes the conversion of galactose-1-phosphate to glucose-1-phosphate. The result is a piling up of galactose-1-phosphate in liver, red blood cells, and other tissues. It has long been known that patients with the disease improve dramatically when placed on a galactose-free diet. Sidbury (73) has explained the

"toxicity" of galactose-1-phosphate by demonstrating its inhibitory effect on another enzyme in the metabolic pathway of glucose, namely, phosphoglucomutase.

Glycogen storage disease.—Attempts to clarify the pathogenesis of glycogen storage disease have been well described in a recent review of medical genetics by Childs & Sidbury (74). The authors describe four types of the disease, each apparently differing clinically and in its enzymatic deficiency but all resulting in glycogen storage. The most commonly encountered defect is a reduction in glucose-6-phosphatase. The resultant hypoglycemia cannot be alleviated by the administration of either glucagon (75) or galactose (76).

Naphthalene sensitivity.—It should be remembered that the newborn infant may express temporary clinical and biochemical abnormalities which are similar to the inherited defects found in older subjects. A fascinating example is the susceptibility of the newborn to napthalene, vitamin K, and other allied drugs. Zinkham (77) has shown that the resultant hemolytic anemia in the immature subject is accompanied by a transient instability of reduced glutathione, similar to the inherited, permanent defect encountered in the primaquine or naphthalene-sensitive adult.

Congenital familial nonhemolytic jaundice with kernicterus.—In 1952 Crigler & Najjar (78) reported 7 cases of a disorder of infants and young children characterized by marked persistent jaundice not due to excessive hemolysis nor to biliary obstruction, and associated with kernicterus; the jaundice was due mainly to indirect bilirubinemia. The authors suggested that in these patients the liver lacks the capacity to convert the insoluble and unexcretable indirect bilirubin into soluble direct form which the kidneys can eliminate. Schmid (79) has recently shown that this conversion consists of an enzymatic conjugation of indirect bilirubin with glucuronic acid. A more recent report by Childs & Najjar (80) shows that kernicterus does not invariably occur in these cases and that its precise relation to the bilirubin disorder requires further exploration. Lacson & Waters (81), by determining urinary hexuronic excretion in infants, and Brown (82), by the use of liver microsomes from guinea pigs, have shown that the conjugating enzyme system gradually develops after fetal life, is relatively inactive in the premature and incompletely developed even in the early newborn fullterm organism. This delay may be related to the common hyperbilirubinemia of the newborn. That the disease in question results from a more severe and lasting permanent enzymatic defect is indicated by its inheritance, persistence, and grave prognosis. It is interesting to find that a strain of rats is known to have the same bilirubin defect, kernicterus, and high fatality rate (83). No useful therapeutic measures are available. Parents of a child with this disease should be warned of its hereditary character, which appears to be a lethal recessive.

Anemia and iron metabolism.—In a review of iron metabolism (84) and subsequent commentary (85) it is stressed that the concept of "iron stores"

in terms of reserve depots is no longer tenable. Rather, iron is present in the circulating hemoglobin. This varies with duration of gestation, placental blood received after delivery, and prenatal factors influencing intrauterine hematopoiesis. Sturgeon's belief that the "placental transfusion" is valuable in increasing available iron (84) does not conflict with the failure of such to demonstrate an acute effect on the neonate's red cell volume or circulating hemoglobin mass (86).

Iron assimilation varies with the hemoglobin level rather than the state of iron stores. This suggests the undesirability of iron therapy in children probably already overloaded, as may be the case in familial jaundice, thalassemia, chronic inflammatory disease, or aplastic or hypoplastic anemia. Josephs (87) states iron depletion in infancy results from weight gain and maximum iron usage. Following depletion, the infant is dependent on current iron absorption. Even on a milk diet this usually is adequate unless other factors make iron unavailable or divert it from hemoglobin synthesis.

Further cases of hypocupremic, hypoferremic, hypoproteinemic anemia are added to these reported by Lahy & Schubert (88) and by Sturgeon & Brubaker (89).

Hypercalcemia.—Daeschner & Daeschner present a case of severe idiopathic hypercalcemia in an infant (90). This is characterized clinically by anorexia, vomiting, constipation, hypotonia, hypertension, mental-motor retardation, and a peculiar "old" appearing face. There is hypercalcemia, azotemia, and impaired renal function. The authors speculate concerning vitamin D sensitivity as an etiologic factor in this disorder.

Lead poisoning.—The incidence of abnormal blood levels of lead in children attending a metropolitan pediatric clinic was found to be extremely high [44.4 per cent of 333 children tested (91)]. The usual screening tests (stippled red cells, long bone films, and coproporphyrinuria) did not correlate well with the blood lead levels and were unreliable. A history of pica was the most reliable single lead to the diagnosis of abnormal lead exposure. The environmental factors involved in lead intoxication in children are complex and require analysis for each individual child if preventive measures are to be effective (92). The treatment of acute lead encephalopathy remains unsatisfactory, with death and permanent neurological disability often occurring (93). Suggestions for optimal therapy and the need for repeated courses of treatment are well presented by the authors of the last article cited.

Dysproteinemia.—Ulstrom and his associates (94, 95) report four cases of transient hypoproteinemia of infants characterized by generalized edema, marked pallor and irritability, severely lowered levels of plasma albumin and globulins, and a form of microcytic, hypochromic anemia, with hypoferremia, hypocupremia but (in contrast to ordinary iron-deficiency anemia) with normal bone marrow. The onset is usually during the early months (but not at birth), and the course is a few weeks ending in full recovery. The cause is not known but is not faulty or deficient food intake.

Extensive studies by the authors led them to the conclusion that the utilization of amino acids is relatively deficient and that there is an abnormally rapid degradation of the plasma proteins. No specific therapy for the hypoprotemia is recommended. Medicinal iron given orally raises the hemoglobin level. The authors regard this rare disease as a "new syndrome"; however, a few similar cases have previously been reported (96, 97).

RENAL DISORDERS

Nephrotic syndrome.—Experience continues to indicate that the signs and symptoms of nephrosis can be controlled with adrenal hormone therapy. The usual initial daily dose is 2.2 mg./kg. of prednisone or prednisolone (98), or 2.2 to 4.4 mg./kg. of cortitrophin (99, 100), continued for 28 days, or until edema disappears and the urine has been free of protein for one week (98). Intermittent long-continued hormone therapy is then instituted in all patients by some authorities (98, 100), or by others (99, 101) only in those who continue to have proteinuria. Such therapy is continued arbitrarily for one year, or its duration may be determined by following the proteinuria, erythrocyte sedimentation rate, or the concentration of complement in the serum. The effect of such therapy on long-term survival cannot yet be determined.

Rothenberg & Heymann (102), on the basis of questionnaires, estimated the annual incidence of nephrosis in Ohio children at 0.5 new cases per 100,000 total population; Cooke (103), using similar methods, obtained the comparable figure of 0.91 for Connecticut children.

Vernier *et al.* (104) report that electron microscopy reveals one characteristic alteration in the nephrotic syndrome regardless of etiology, namely, flattening and coalescence of the foot-processes of the glomerular capillary epithelium. This change has also been observed by Piel *et al.* in nephrosis (105) of childhood and in experimental nephrosis induced in rats with nephrotoxic rabbit serum (106). Vernier *et al.* (104) have performed approximately 100 renal biopsies by percutaneous needle aspiration with success in 75 per cent. This report indicates that renal biopsy is as safe and expedient a procedure in childhood as previously repeatedly reported in adults.

Hypertension.—Daeschner *et al.* (107) report the use of reserpine as an antihypertensive rather than a hypotensive agent. For hypertension associated with acute nephritis doses of 80 to 150 μg./kg. of body weight were safe and effective. Rarely did they have to use hydralazine in combination with reserpine as described by Etteldorf, Smith & Johnson (108).

Tubular nephropathies.—Reviews of diseases of the renal tubules in childhood have recently appeared in the pediatric literature (99, 109). Piel & Harper (110) report that children with generalized amino aciduria of the Fanconi and Lowe syndromes show clearance of intravenously administered D and L methionine like that of normal individuals, thus indicating a minimal renal abnormality which is in complete contrast to the virtually total

lack of evidence for a tubular transport system for cystine and lysine demonstrated in "cystinurics." The clearance of both of these amino acids has been shown by Dent *et al.* (111) and by Doolan *et al.* (112) to be equal to that of inulin.

Of particular interest is the paper of Cogan *et al.* (113) which is probably the first well-documented report of the presence of cystine storage disease in an adult. In addition, there was no evidence of reabsorptive defects of the renal tubule, an unusual finding in cases of cystinosis.

MISCELLANEOUS CONGENITAL DISORDERS

Congenital Heart Disease

Surgery.—In the field of congenital heart disease the outstanding development of the past year has been the mushroom growth of intracardiac surgery with the pump-oxygenator. Dr. John Gibbon's infant heart-lung machine of twenty years ago has evolved into a complex of "filmers," (114, 115), bubblers (116, 117), and a transmembrane oxygenator (118, 119). While the proponents of each type of machine have been debating their respective merits, several surgical groups have presented rather long series of operations for closure of ventricular septal defects, resection of pulmonary stenosis, and correction of the rarer congenital abnormalities. Surgical mortality has varied roughly from 40 per cent to 10 per cent, depending largely on the type of lesion (117, 119, 120, 121). The stopped-heart technique, developed by Melrose (122) using potassium, and Lam (123) using acetylcholine, has been widely accepted as an important advance in surgical technique (124, 125).

The cause-and-effect relation of increased pulmonary blood flow to pulmonary hypertension is still under discussion (126, 127), although it seems clear that any large increase in pulmonary vascular resistance greatly increases the hazard of closing intracardiac shunts.

In the meantime, mortality from the older techniques of cardiac surgery is steadily decreasing. Glenn *et al.* (128) have reported 110 closures of patent ductus arteriosus without mortality. Swan's group has reported 46 cases of atrial septal defect closed under hypothermia with a mortality of 7 (129), and Kirklin *et al.* have reported 71 cases closed by the well technique with a mortality of 4 per cent (130). Similar low mortalities are reported by practitioners of the purse-string technique (131).

Diagnosis.—In diagnosis, although the cardiac catheter still is king, there has been increasing interest in angiocardiography by more rapid techniques (and more expensive instruments), and in other electronic aids such as phonocardiography (132, 133), ballistocardiography, and vectorcardiography (134). "The acyanotic tetralogy" is emerging as a common variant of the intraventricular defect (135) and as perhaps a stage in the natural history of the tetralogy of Fallot (136).

Familial dysautonomia.—First clearly delineated as a clinical entity in 1949 by Riley, Day *et al.* (137), some 69 cases of this rare familial disease

have now been collected by Riley (138), virtually all Jewish. In affected families 25 to 30 per cent of siblings have been affected but none of the known forebears. Constant and pathognomonic features, almost all nervous, are: (*a*) autonomic disturbances, such as reduced or absent tears, periodic vomiting, thermolability, excessive perspiration, postural hypertension, and cold extremities; (*b*) disturbances of the voluntary neuromuscular system such as absent or hypoactive deep tendon reflexes, poor motor co-ordination, dystarthria, and impaired swallowing reflex; (*c*) sensory disturbances, such as relative indifference to pain and corneal anesthesia; (*d*) faulty psychological equilibrium, such as emotional lability, breath-holding spells in infancy, and apparently reduced intelligence. Retarded growth is fairly common, as are attacks of bronchopneumonia. Cardiac arrest occurred in two cases during anesthesia. Autopsy studies have not revealed an anatomical basis for the clinical manifestations. Of various therapeutic measures that have been tried, none has been decisively helpful to the patients. Group therapy for the emotional problems of parents has been useful in New York City where most of the cases have occurred. The emotional problems of the children seem to lessen with time and some patients may learn to adapt themselves to society.

Cystic Pancreatic Fibrosis

The clinical variants of cystic pancreatic fibrosis still are not sufficiently appreciated. Di Sant'Agnese (139, 140), summarizing current concepts, describes five clinical pictures. Most children with cystic pancreatic fibrosis have both chronic digestive disability and such pulmonary manifestations as emphysema, bronchopneumonia, or lobar atelectasis. A few manifest pancreatic insufficiency without apparent pulmonary involvement. Some children, without digestive disability apparent, initially manifest pulmonary changes progressing to complete insufficiency. Evidences of cirrhosis and portal hypertension may first draw attention to the disorder as, also occasionally, heat exhaustion may be the presenting complaint. More than 95 per cent of infants and children with cystic pancreatic fibrosis show an increased concentration of sweat electrolytes. Cystic pancreatic fibrosis should be considered in the diagnosis of children with idiopathic bronchiectasis (141).

Various modifications of the sweat electrolyte test (142), and further evidence of the unreliability of saliva electrolyte studies (143), include a report of the simple use of hand or foot prints on agar surfaces containing the test ingredients described by Shwachman *et al.* (144). Determinations of the salivary iodine content after oral lipiodol may be a useful screening test (145).

Reemtsma *et al.* (146), studying I^{131}-labelled neutral fat and fatty acid absorption, found dissociation in fatty acid absorption between children with cystic pancreatic fibrosis and adults with pancreatic insufficiency sec-

ondary to resection or fibrosis as further evidence of the generalized disability in this disorder.

Bruck (147) reports decreased arterial oxygen concentration earlier than the anticipated carbon dioxide retention even with minimal clinical evidence of respiratory involvement. In more advanced pulmonary involvement, oxygen therapy further depressed respirations and exaggerated CO_2 retention as in adults with chronic respiratory acidosis. Studies of compliance, resistance to air flow, and residual lung volume in children with cystic pancreatic fibrosis, reported by Cook *et al.* (148), should facilitate better evaluation of therapeutic measures applied to the usual pulmonary disability.

RESPIRATORY PROBLEMS OF THE NEWBORN

A well-controlled clinical study of the use of the Bloxsom Air Lock as a resuscitator in premature infants born by nonelective cesarean section demonstrated no value for the Air Lock (149). An equally well-controlled clinical study on the effects of water vapor mist on respiratory distress among infants born to diabetic mothers demonstrated that mist per se did not alter the mortality or morbidity among these infants (150).

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DISEASES OF BONES AND JOINTS[1]

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RHEUMATOID ARTHRITIS

Studies in the pathology of rheumatoid arthritis have indicated that widespread changes occur in the joints and mesenchymal tissues, and that these changes are pleomorphic and not necessarily specific in nature. Sinclair & Cruikshank (1) have studied in detail 16 of 90 cases coming to autopsy, examining in particular the visceral lesions which were widespread in the group. They found endocardial damage in eight cases, and myocardial changes in five; acute pericarditis was present in one, and healed pericarditis in three cases, obliteration of the pericardial space being present in three others. Pleurisy was present in 12 cases and was presumably related to the arthritis, while lymphadenopathy occurred in four and amyloidosis in four. Histologically, the visceral lesions were of three kinds, granulomata, nonspecific inflammatory lesions containing predominantly round cells, plasma cells, histiocytes, and polymorphonuclear cells, and amyloid deposits. The authors review the literature on visceral lesions in rheumatoid arthritis and express the opinion that the arthritis is part of a generalised "rheumatoid disease" and come to the interesting conclusion that the available evidence does not justify the inclusion of this type of arthritis among the so-called "collagen diseases." Their argument is based on the known impossibility of pointing to a common basic change in all the affected sites, the fact that there is a difference of opinion among authorities regarding the part played by collagen in the granuloma of rheumatoid disease, and about the composition of fibrinoid which is one of its main features, and they conclude that at the moment it does not seem possible to explain all of the lesions of this disease on the basis of a primary abnormality of collagen.

Sokoloff (2), in a study of the pathological findings in the hearts of 113 cases with rheumatoid arthritis studied postmortem, found a variety of lesions including (*a*) rheumatic heart disease; (*b*) pericarditis; (*c*) granulomatous inflammation in the valves and pericardium resembling that of the subcutaneous nodule of rheumatoid arthritis; (*d*) coronary arteritis; (*e*) interstitial myocarditis; and (*f*) calcareous stenosis of the aortic valve, there being no cases of aortic insufficiency encountered in this group. He is of the opinion, on the basis of this study, that there is a type of heart disease in patients with peripheral rheumatoid arthritis which can be distinguished from rheumatic heart disease morphologically, that the incidence of rheumatic heart disease in rheumatoid arthritis is not so high as has been thought in the past, and that the pericardial obliteration which is commonly

[1] The survey of the literature pertaining to this review was concluded in August, 1957.

observed in this type of arthritis appears to be a manifestation of rheumatoid heart disease.

The sheep cell agglutination test has been found positive in as many as 89 per cent of cases of rheumatoid arthritis, depending upon the method used, and is positive in some patients with collagen disease, especially systemic lupus erythematosus. It is usually negative in patients with rheumatoid (ankylosing) spondylitis, arthritis associated with psoriasis, juvenile rheumatoid arthritis, gouty arthritis, rheumatic fever, and degenerative joint disease. The agglutination of sheep red cells sensitised with antisheep haemolysin by rheumatoid serum has been the subject of continuing investigation.

Several papers presented at the annual meeting of the American Rheumatism Association in 1956 highlighted the results of these studies. In an endeavour to isolate the sheep cell agglutinating factor, Lospalluto & Ziff (3) fractionated serum from patients with rheumatoid arthritis by a number of methods. On precipitation with ammonium sulphate, the agglutinating factor was obtained at concentrations of salt between 1.2 and 1.4 *M*. This fraction yielded an active euglobulin when dialysed at pH 7. Treatment of this euglobulin by cold globulin precipitation yielded a fraction which contained all the agglutinating activity of the original serum in 1.6 per cent of the original nitrogen, a purification of about sixtyfold. Electrophoresis of this product revealed the presence of at least two components with mobilities in the gamma and beta globulin range. An inhibitor of the sheep cell agglutination was demonstrated in rheumatoid as well as in nonrheumatoid sera in globulin fractions precipitating at concentrations of ammonium sulphate higher than 1.4 *M*. Using ion exchange chromatography, these workers were able to obtain the agglutinating factor in fractions purified more than five hundredfold.

From this investigation it would appear that although the agglutinating factor occurs almost specifically in the serum of patients with rheumatoid arthritis, the inhibitor is present in all human sera, and does not seem to be concentrated in any single globulin fraction. However, the experimental data suggested that the inhibitor was present in insufficient amount in the serum to modify the agglutination titer of rheumatoid sera.

Epstein, Johnson & Ragan (4) approach the problem of characterising the "rheumatoid factor" present in positive serum from a slightly different angle by omitting the sensitized sheep cells from the test and using instead pooled human gamma globulin combined with the serum of patients having rheumatoid arthritis and a positive Fraction II test. This test uses tannic acid-treated sheep red cells coated with pooled human gamma globulin and suspended in various dilutions of the patient's serum. These workers confirmed the fact that precipitates do form in these circumstances, and carried out dilution studies which revealed characteristics of an antigen-antibody system involving some of the constituents of the pooled human gamma globulin acting as antigen, and the rheumatoid factor acting as antibody.

Further studies indicated that the antigen constitutes only a small fraction of the total gamma globulin.

Another study reported by Plotz & Singer (5) was an endeavour to avoid the use of sensitized sheep cells and other particles having biological properties. They used polysterene latex particles mixed with commercial gamma globulin, adding the mixture to progressive dilutions of serum from patients with rheumatoid arthritis until a typical agglutination reaction occurred. Of a large number of patients tested, 100 were suffering from rheumatoid arthritis. When tested by this technique, and by the sheep red cell agglutination and other tests, the percentage of positive results was found to be almost identical for all methods used. Twelve patients who were negative to the red cell agglutination test were positive to the so-called "Latex fixation test," and 4 patients with 1:64 red cell agglutination titers were negative to the latex fixation test. It was found that, using this latter method, there was no "doubtful" group as the latex fixation test was either positive or negative. False positive results were less than 2 per cent and therefore comparable with other methods. This test limits the biologically active factors to gamma globulin and the serum to be tested, and again the findings suggested that the agglutinating factor in the serum of patients with rheumatoid arthritis may be an autoantibody against gamma globulin.

Ziff (6) points out that these investigations seem to indicate that the essential reaction involved in all of these tests is one in which the rheumatoid factor reacts with a constituent of the gamma globulin, regardless of its source, but whether or not the agglutinating factor is an antibody remains to be proven. The various tests have been set out conveniently by Ziff (7).

In treatment, the benefits of rest, physical therapy, splinting of joints when necessary, and adequate diet are accepted generally as an essential part of the basic regimen. Acetylsalicylic acid (ASA) has held its own in the treatment of rheumatoid arthritis and Bauer & Ropes (8) suggest that it should form part of the basic regimen, while Holbrook, Hill & Stephens (9) recommend it for its pain-relieving properties. Bachman, Calkins & Bauer (10), studying the metabolic effects of ASA in five patients, noted that on doses of 3.3 to 6.0 gm. the minute volume of ventilation increases, the total plasma CO_2 content decreases, and the serum pH rises slightly. These doses were found to control joint swelling, pain, and stiffness in these patients.

The Empire Rheumatism Council Research Subcommittee (11) reported a further multi-centred controlled trial to compare the effects of cortisone acetate and ASA in the long-term treatment of cases of rheumatoid arthritis. They chose cases of all durations and investigated 100 patients of whom 38 on cortisone and 39 on ASA completed one year of therapy. Patients between the ages of 17 and 60 years, with three or more involved joints, were chosen. Fixed flexion deformity, mental instability, gastric disease, and hypertension were not present in any of the cases. Treatment

included the basic regimen with either cortisone or ASA, and cortisone dosage was adjusted to the lowest dose which would control the symptoms, being discontinued if 100 mg. or more was required in any case for more than a month. The lowest dose of ASA was also given, and at the end of 1 year the mean dose of cortisone administered was 69 mg. daily, and of ASA 59 gr. (4 gm.). Twenty-two patients were withdrawn from the trial during the year because of toxic symptoms, failure to benefit from therapy, or failure to attend, and one patient did not start treatment. These factors affected both groups equally. Using criteria which they discuss in detail, the committee concluded that there was no significant difference between the two groups at the end of the period, except that at 2 months the sedimentation rate was lower and at 6 months the Hb level was higher in the cortisone-treated patients.

There is general agreement that cortisone and hydrocortisone may suppress the clinical manifestations of rheumatoid arthritis but the dosage required is often dangerous. The recognition that serious side effects can occur has stimulated the search for derivatives which might give rise to fewer reactions. In 1955, Bunim, Pechet & Bollet (12) reported an investigation of prednisone and prednisolone, which are derivatives of cortisone and hydrocortisone, respectively, in which dehydrogenation in the 1,2-position has been accomplished to produce the δ-1 compounds of the above steroids. They studied a group of seven patients and found that both substances had the activity of adrenal cortical hormones in that they decreased the circulating eosinophil count and the urinary 17-ketosteroid output. They controlled effectively the clinical manifestations of the arthritis and reduced the inflammation of the synovial membrane. Using prednisolone, it was found that hemopoietic stimulation occurred in several patients, the haematocrit, haemoglobin level, red and white cell counts all rising, while the sedimentation rate fell to normal. Balance studies on two patients showed that using 30 mg. daily of prednisolone caused no sodium retention, and no potassium or nitrogen loss. When a dose of 50 mg. was used in one case, a negative nitrogen balance developed. These investigators (13) subsequently described peptic ulcer symptoms, mental depression, and alterations in the glucose tolerance as possible side effects of these steroids.

Boland (14) used these drugs over a period of six to nine months in 141 cases of rheumatoid arthritis which were moderately severe and of an average duration of 126 months. Prednisone was used in 78 (55 per cent) and prednisolone in 63 (45 per cent) of the patients, although in a few medication was changed transiently from one steroid to the other to allow comparison of response and dosage requirement. Analysis of the results showed that treatment had been discontinued in seven because of remission, and in 12 because of lack of improvement or owing to serious complications. The general conclusions from the study were that in the group as a whole 50 per cent of patients maintained major improvement during the six to nine months, although improvement was always most marked in the first

2 months and then slowly declined till the 8th month. Maintenance doses of either steroid, in moderate cases varied between 5 and 15 mg. daily, and severe cases required 20 mg.

Adverse reactions were noted in at least 50 per cent of the cases treated but were only severe enough to lead to discontinuance of treatment in 16 cases. The major reactions were gastric symptoms suggesting peptic ulcer, purpuric and ecchymotic rashes occurring on arms and legs, and vasomotor disturbances such as hot flushes in women. Cushingoid symptoms arose as with other steroids, but edema and hypertension were rare. A comparison of the potency of prednisone and hydrocortisone indicated that prednisone is roughly 4 times as potent as hydrocortisone when used as an antiinflammatory agent, and that prednisone and prednisolone appear equally potent. Neustadt *et al.* (15) treated 16 cases of rheumatoid arthritis with prednisone and prednisolone, with improvement in 12. The anemia and white blood counts were not influenced in this series, but the abnormal sedimentation rates and albumin-globulin ratios returned toward normal. Relapses in the clinical state occurred when the steroids were withdrawn, suggesting that their effect is a suppressive one. Hart *et al.* (16) recorded similar results and were of the opinion that prednisone and prednisolone are superior in effectiveness to cortisone. As a result of recent studies with these steroids, Bunim, Black & Yielding (17) point out that if patients cannot be controlled satisfactorily with maintenance doses of 15 mg. of prednisone daily, they should be considered unsuitable for this form of therapy. Many, however, feel that 10 mg. daily is the maximum safe dosage.

The search for therapeutic agents for use in rheumatoid arthritis continues and the antimalarial drugs are still receiving attention. Recently chloroquine sulfate and phosphate have been advocated as remedial agents, and Freedman (18) treated 54 cases with chloroquine sulfate 300 mg. daily for 2 years. Forty-three patients so improved that they had no stiffness and no clinical evidence of joint inflammation, although some did have pain from joints affected by secondary degenerative change. Three patients continued to have slight joint inflammation, three had to discontinue treatment in the early stages because of inadequate response, and one still had active disease in spite of chloroquine. Two patients in the group defaulted after one year as they were improved, and one elderly patient died with a psychosis, probably unrelated to therapy; a further patient died of nephritis 5 months after discontinuing therapy. In the early stages of the trial all the patients received 40 grs. of ASA and 200 mg. of ascorbic acid, which makes it somewhat difficult to assess the true value of the drug. Rinehart (19), in a study of young persons between 3 and 22 years of age, administered 250 mg. of chloroquine twice daily, and found that eight of 11 improved or went into remission, while eight of 14 older patients improved but did not show remission.

Bagnall (20) has treated 125 private patients suffering from rheumatoid arthritis with chloroquine for more than 4 years. Chloroquine diphosphate,

250 mg., was given daily at bedtime, and remissions or major improvement occurred in about equal numbers of 71 per cent of patients. Concomitant therapy was not withheld in the early stages to bridge the gap of one to three months before chloroquine begins to act. He found that factors such as duration and severity of the disease play their expected parts in the results. The toxic symptoms encountered were: dermatitis in 35 per cent of cases; forty per cent of those developing skin rashes were unable to resume full dosage of chloroquine; "seasickness," which included nausea, giddiness, frontal headache, and blurred vision, occurred in 32 per cent of cases, but subsequently did not prevent 90 per cent of those in whom it occurred from taking full doses later; leucopenia but not agranulocytosis occurred in 4 per cent of patients; metrorrhagia, lymphedema of the forearm and hand, and symptoms reminiscent of serum sickness were rarely encountered.

RHEUMATOID (ANKYLOSING) SPONDYLITIS

The problem as to whether or not there is a difference between rheumatoid spondylitis and ankylosing spondylitis has not been settled, but several reports have concerned the incidence of cardiac lesions in cases of spondylitis. Clark, Kulka & Bauer (21) describe 22 cases presenting aortic regurgitation, either alone or accompanied by mitral stenosis, and give details of nine cases coming to autopsy. All the cases were males, and syphilis and rheumatic fever did not appear to be etiological factors in the valvular lesions. Congestive failure occurred in 10 of the cases and angina pectoris in eight.

The aortic valves were dilated and the cusps were thickened, retracted, and presented rolled edges, the commissures being separated; discrete intimal plaques occurred on the valve commissures and aortic intima, while focal calcification was present in the valves in some. The microscopic changes consisted of focal destruction of the media with necrosis of muscle fibres and fragmentation of the elastic lamellae, accompanied by ingrowth of vascular granulation tissue containing lymphocytes, small mononuclears, wandering cells, and neutrophils. These changes occurred in the aorta and valve cusps alike, and the adventitia showed varying degrees of perivascular round cell infiltration, connective tissue proliferation, mucinous edema, and fibrosis. The myocardium and pericardium adjoining the valves also showed changes.

A distinction from rheumatic aortic valve disease was made because spondylitic valvulitis showed little tendency for the valve cusps to fuse, while fibrosis of the myocardial septum, fusion and thickening of the chordae tendineae, and fibrosis of the left auricular endocardium was rarely found, and the intimal plaques found in spondylitis are never seen in rheumatic valvulitis. Although the spondylitic lesions were found to resemble syphilitic aortitis, the distinctive lesions remain discrete, do not extend distally beyond the ascending aorta, and the multi-nucleated giant

cells found in syphilis do not occur in spondylitic aortitis, although the resemblances are close in these two conditions. The importance of this condition is stressed as in so many cases the cause of death is cardiac. Shilder, Harvey & Hufnagel (22) also describe five cases of spondylitis associated with aortic valve lesions, with two autopsies showing similar lesions in the aortic valve.

Another interesting problem has arisen with the description of the possible occurrence of leukemia from radiation therapy, and Brown & Abbatt (23) in a preliminary report studied the data from 9364 cases of spondylitis treated with deep x-ray therapy at 37 centers in Great Britain. They found that of 4297 patients whose sex was recorded, 3679 were males, 618 were females, and 92 per cent were between 15 and 54 years of age. It was found that of 3085 attending 17 centers, 1731 (56 per cent) patients were returning periodically for examination or had died, while of 2361 patients, 797 (33.8 per cent) had had more than one course of treatment. At this report 25 patients had developed leukemia, but this figure, it was pointed out, was probably incomplete as only about 44 per cent of the 9364 had been under continuous observation. Of these 25 patients, 21 had died of leukemia and, in 4 cases, spondylitis and leukemia were thought to co-exist at the time of radiation.

The authors have calculated from the Registrar-General's returns for death rates for leukemia for the period 1940–53, that among 9364 individuals of the same age group, the expected number of deaths from leukemia would be 5.4 to 1, while if only those cases which were followed up are included the ratio rises to 9.5 to 1.

While these authors recognize that spondylitis and leukemia can co-exist before radiation they conclude from this study that x-radiation plays a real part in producing leukemia. They suggest, however, that this type of therapy is valuable in suppressing symptoms and is not, therefore, contraindicated, although they do stress that repeated treatments be avoided if possible. Abbatt & Lea (24) in a further study of this problem take the view that radiation therapy plays an important part in the production of leukemia in these cases.

In another interesting study, Pillers & Marks (25) carried out bone marrow studies in 28 patients with spondylitis. They found hypercellularity of the marrow in five of 10 cases who had had one or more courses of radiation therapy, and in six of 18 cases who had had no previous therapy, suggesting that the hypercellularity is not related to previous therapy. The myeloid-erythroid ratio was normal in both groups, and this further suggested that the bone marrow had not been stimulated by radiation in the doses given. The increased cellularity affected all the cells in the marrow, and both myeloid and erythroid cells showed normal maturation. There was, however, an increase in plasma cells in 10 patients, and an increase in the eosinophils in four. These observations are interesting as they indicate that the stage is set for the cellular proliferation to exceed normal bounds, either

from stimulation by x-rays or from other causes not obvious at present.

In a similar study, Stewart & Dische (26) examined the marrow from 28 cases and found 39 per cent with hypercellularity before therapy. They noted, however, that with a dose of 1020 to 1640 r the marrow became hypoplastic in the areas treated, this condition persisting for periods extending to 6 months after treatment, and then returned slowly to the hypercellular state thereafter. This would suggest that lower doses of x-ray may not lead to bone marrow stimulation.

Because of the obvious importance of this subject, Kellgren (27) has studied a series of 500 cases of spondylitis and found that about 75 per cent appeared to have typical rheumatoid (ankylosing) spondylitis. The remaining 25 per cent appeared to have other forms of polyarthritis with spinal involvement, especially rheumatic fever, Reiter's syndrome, rheumatoid arthritis, and arthritis associated with psoriasis, and that these forms are not benefited by x-ray therapy. The recognition of these atypical forms of spondylitis is important, since the risk of leukemia and severe anemia following radiation therapy may have serious consequences. This form of treatment should not be given to these patients.

GOUT

The cause of hyperuricemia in primary gout is still uncertain. Most seem to favour the view that there is an overproduction of uric acid but the possibilities of diminished uricolysis or impaired renal excretion are under constant review. Excellent reviews of biosynthesis and metabolism of purines have been given by Stetten (28) and Wyngaarden (29), and the latter has produced data suggesting that the hyperuricemia may be owing to excessive production of uric acid through a normal biosynthetic process. However, there is some evidence that there may be more than one way in which urate synthesis occurs, and in order to investigate a possible "shunt mechanism" for urate biosynthesis which some gouty patients appear to have, the mechanism has come under scrutiny in recent years. Seegmiller *et al.* (30) have studied a series of normal and gouty individuals using 4-amino-5-imidazole carboxamide (AIC). This substance has been shown, in animals and bacterial systems, to become incorporated into purines at some stage of the biosynthetic chain between glycine and uric acid. AIC was synthesised with C_{13} in the four position and fed to human subjects to learn more of the suggested "shunt mechanism."

They found in two normal males that 23 per cent of the administered dose was incorporated into the urinary uric acid and 20 per cent recovered unchanged in the urine. It was concluded that the AIC was incorporated into the uric acid rapidly but that there was an additional contribution of isotope to uric acid from a body pool with a slow turn-over rate, presumed to arise mainly from tissue purine. A pool of free AIC-C_{13} was not detected in the body. Glycine-N_{15} was fed with AIC-C_{13}, and the AIC-C_{13} appeared capable of inhibiting the *de novo* synthesis of uric acid from glycine.

Similar studies in patients with gout who showed the normal incorporation of N_{15} into uric acid suggested that there was an increased incorporation of AIC-C_{13} into uric acid, but this was not sufficiently marked to provide conclusive proof of a shunt mechanism although it was suggestive. They did find some similarity between gouty and normal individuals with regard to AIC-C_{13} incorporation.

In view of these findings, Wyngaarden has suggested that there may be two biosynthetic mechanisms for producing urate in man, that is, a slow, indirect pathway of uric acid synthesis involving the classical scheme of oxidation of free basic xanthine to uric acid as the final synthetic step, and a more rapid direct mechanism as described above. He postulates that the defect, at least in some patients with primary gout, may involve the more direct of these mechanisms.

It has been observed that although humans lack uricase, they do possess at least two other enzyme activities capable of degrading urate, namely, verdo-peroxidase in the white blood cells, and cytochrome oxidase and peroxidase activity in the red blood cells. In this connection Bien & Zucker (31) performed a series of experiments in normal and gouty individuals in which they incubated whole blood, plasma alone, and plasma containing either white blood cells or red blood cells from each individual. They found that uricolysis occurs in whole blood and in plasma containing white or red blood cells, but not in plasma alone. The rate of uricolysis was diminished in gouty individuals and might therefore contribute to the hyperuricemia in these cases. They also showed that the rate of uricolysis was unchanged in normal plasma, containing cells, to which urate had been added to make it hyperuricemic, suggesting that the hyperuricemia of gout is not responsible for the diminished rate of uricolysis in these cases.

Tannhauser (32) favours a renal basis for the hyperuricemia of gout. Basing his argument on the modern concepts of renal function which postulate that the kidney excretes solutes mainly via the glomeruli and selectively reabsorbs the filtered substances through the tubules, he suggests that in normal man the conditions for uric acid elimination are constitutionally unfavourable because 90 per cent of the uric acid is reabsorbed from the glomerular filtrate. Increased tubular reabsorption in gouty individuals may then aggravate these constitutionally unfavourable conditions for uric acid elimination, leading to hyperuricemia and eventually urate deposits. He does not, however, produce any new evidence of a renal disorder to support this view.

The genesis of the acute attack of gout is as obscure as the cause of the hyperuricemia. Sokoloff (33) points out the objections to the view that hyperuricemia is the cause of the acute attack: (*a*) in chronic tophaceous gout, in which large amounts of urate are deposited, acute inflammatory reaction may be conspicuously lacking; (*b*) hyperuricemia produced by intravenous injection of uric acid into normal and gouty subjects has failed to precipitate acute gouty arthritis; and (*c*) colchicine which specifically

suppresses acute gout does not affect synthesis or excretion of uric acid, while probenicid which does increase elimination of uric acid does not affect acute gout. He describes a case in which biopsy of the synovial membrane of a joint in the acute stage was examined and needle-like crystals found. This, together with the observation of Zeveley *et al.* (34), suggests that urates are deposited in the articular tissues during acute attacks, although this does not prove that these deposits cause the acute inflammatory reaction.

In regard to treatment, the acute attack may best be controlled with colchicine, either given by mouth in 0.5 or 1 mg. doses every hour until the attack is brought under control, or diarrhoea, nausea, and vomiting occur, or by intravenous injection in doses up to 3 mg. which will often abort the attack. Lockie (35) advocates the use of phenylbutazone, 200 mg. every 2 hr. for 3 or 4 doses combined with colchicine, 0.5 mg. with each dose, and this may be repeated the next day if necessary. ACTH gel given in doses of 100 mg. intramuscularly daily will often control attacks. Rest and a bland diet are necessary during the attack. For control of chronic gout a diet of low purine value would seem to have some value. Colchicine in doses of 0.5 mg. daily in the interval between attacks has been found to reduce them, while probenecid and other uricosuric agents have been found not only to reduce the frequency of attacks, but, in the case of probenecid, to reduce even the size of tophi. This drug is usually administered in doses of 1 to 2 gm. daily over long periods and is not necessarily contraindicated in cases with renal damage.

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PLASTIC SURGERY: HOMOTRANSPLANTATION, CONGENITAL ANOMALIES, WOUND HEALING, AND SKIN STORAGE[1]

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The authors of the most recent review of advances in plastic surgery emphasized wound care and skin grafting. During the intervening five years, other topics of equal interest and importance have been reported and deserve review at this time. These include a better understanding of the problems of homotransplantation, further evidence of factors responsible for the occurrence of congenital anomalies, analysis of the changes in the wound during healing to learn more of this mysterious process, and perfection of methods for prolonged storage of skin in "banks."

Homotransplantation

Current studies of the nature of individual tissue specificity were stimulated by the important observation of Medawar (1) that a second skin graft from the same donor rabbit to the same recipient rabbit was rejected more rapidly than the first. This evidence of specific sensitization of the recipient by the donor tissue has stimulated hope that a recognized biological reaction may explain the mysterious "individual tissue specificity" originally theorized by Loeb (2).

The terms "homostatic" and "homovital" have been coined by Longmire (3) to differentiate structural transplants, bone, cartilage, blood vessels, etc., whose purpose is to supply framework only, from transplants of skin, kidney, or endocrine tissues whose usefulness depends upon permanent survival of the cells of the transplant. It is in the latter group that the rejection response is elicited.

The local reaction to a skin homograft is marked by edema, leucocytic infiltration, predominantly lymphocytic, slowing of the blood flow locally and, finally, dissolution of the graft. These changes have been observed *in vivo* by transillumination of the graft in a transparent chamber (4) or by direct observation with a dissecting microscope (5). In the homotransplanted kidney similar cellular infiltration is observed with swelling of the endothelial cells of the cortical vessels, tubular degeneration, and necrosis without glomerular changes (6). The picture of the local response in the host and the graft resembles that of an antigen-antibody reaction.

The "second set" phenomenon, the term used for the accelerated rejection of a second graft from the same donor to the same recipient, is very

[1] The survey of the literature pertaining to this review was concluded in June, 1957.

specific between animals even of the same species. The still unidentified antigen is shared by many tissues of the same individual—skin, leucocytes, lymphoid tissue, kidney, and lung. The homograft can be protected from destruction in a number of ways. Skin homografts to areas devoid of lymphatics (brain or anterior chamber of the eye) fail to elicit a response because the antigen is not absorbed into lymphatics, but if the host is specifically sensitized by the antigen from another graft to an area with lymphatics, a local reaction is initiated at the site of the primary graft which will destroy the graft. In the Algire diffusion chamber (7) skin homografts will survive even in an immunized host because the porous walls of the chamber exclude the immunized host cells which alone can destroy the homograft. Egdahl & Hume (8) have established sensitization of dogs by temporary cross-circulation. A vascularized kidney homotransplant between this sensitized pair will be protected from rejection and continue to function if cross-circulation is re-established at the same time. Rapid necrosis of the homo-grafted kidney occurs when the cross-circulation is discontinued. Dilution or destruction of antibodies produced by the recipient is thought to abort or delay the rejection reaction.

The evidence at present strongly supports the concept that rejection of a homotransplant occurs because of a specific host sensitization by an antigen present in the transplanted tissue which is absorbed into the lymphatics of the host.

Permanent survival of homotransplanted skin (9) and kidney (10) has been reported between identical twins. The life-saving use of a kidney homotransplant has been carried out with dramatic success in four sets of identical twins at the Peter Bent Brigham Hospital. Prolonged and possibly permanent survival of skin homografts has been reported in humans who, because of agammaglobulinemia, are incapable of producing antigens either to bacteria or foreign skin (11).

In the naturally occurring, dizygotic freemartin cattle (12), twins of opposite sex which develop from separate germ cells, both skin and kidney have been exchanged successfully. An intermingling of fetal circulation, proven by identification of circulating blood cells of dual origin, establishes a permanent tolerance early in embryonic life. Billingham (13) has induced "acquired tolerance" by intrauterine injection of homologous cells within the mouse fetus. Tolerance to skin homografts established by this method is donor-specific and not due to a change in the recipient's immunologic response.

Booth *et al.* (14) have recently reported the existence of blood cells of dual origin in adult human twins of opposite sex. The authors conclude that there are connections between placental blood vessels during gestation. No exchanges of tissue have been reported, but permanent survival is a probability. When the phenomenon occurs in cattle, the female is sterile. Each of the two women reported by Booth has had three children.

Increases in survival time of homografts have been reported by reduc-

tion of the antigenicity of the graft or by the responsiveness of the host, but no permanent survivals have been achieved. Experimental "immunoparalysis" (15) by repeated grafting from the same donor to the same recipient and by nonspecific homologous skin extracts (16) has been reported.

Thus, current evidence (17) indicates that the rejection of homovital transplants occurs on the basis of an antigen-antibody reaction which is host- and donor-specific but not tissue-specific; that permanent survival of skin and kidney transplants is possible only between identical twins and in patients whose immune response is deficient because of agammaglobulinemia; that acquired tolerance may be induced by intrauterine injection of the fetus with homologous cells or by the natural sharing of fetal circulation as in pairs of dizygotic freemartin cattle; and that the duration of survival of homografts may be prolonged by altering or suppressing the host antibody response or by reducing the antigenicity of the transplant.

Congenital Anomalies

Man has always been interested in the causes of deformities in his offspring. Tales of maternal impressions which have come to us in ancient legends are still reported by our patients. The experimental production of congenital defects by exposing the pregnant female to stresses at precise intervals following conception may return the disdained idea of maternal impressions to a respected place.

One of the early evidences that anomalies are acquired as well as inherited was Gregg's (18) observation that congenital cataract in infants was linked to an epidemic of rubella. This observation has been confirmed by other reports since that time (19, 20). Warkany (21) succeeded in producing cleft palate experimentally in the rat embryo by withholding riboflavin from the mother's diet. Baxter & Fraser (22) reported a 44 per cent incidence of cleft palate in the offspring of mice treated with cortisone.

Among the most fruitful investigators have been Ingalls *et al.* (23), who succeeded in producing and reproducing specific deformities by subjecting the mouse fetus at various stages of prenatal development to a variety of insults, including anoxia, x-radiation, and cortisone. He has determined the degree of tolerance of the mother and the unborn litter to anoxia and hypoxia. Too prolonged or too high a degree of anoxia results in a costly embryonic mortality. Lesser degrees will not destroy the litter but will induce a variety of malformations. The timing of exposure to anoxia is critical—thus, cleft palate in the mouse is produced by anoxia on the 14th to 15th day of gestation. X-radiation at the same stage will induce cleft palate. According to Kalter & Fraser (24) hydrocortisone acetate administered to the mother over a critical period of four days will induce cleft palate in the young. Ingalls & Curley (25) narrowed the exposure interval to a single dose or a single day, the 12th day of gestation. A difference of two days in the critical exposure time to anoxia or radiation and to cortisone acetate administration is interpreted as a reflection of the relative speeds at which

the processes act. Rapidly differentiating tissues are more susceptible than resting or mature cells.

Two human cases of cleft palate were reported in 1956 in which cortisone had been administered to the mothers during the first two months of pregnancy (26, 27).

Translating the stage specific evidence to the human, Ingalls considers that cyclopia (one eye) can be expected to occur in the first week of pregnancy, conjoined twins in the second, extromelia (absent extremities) in the third, tracheoesophageal fistula in the fourth, nuclear cataract of the lens in the fifth, harelip in the sixth, cleft palate in the seventh, mongolism in the eighth, and other types of soft tissue and brain damage in later pregnancy. He emphasizes that other unknown factors of susceptibility are certainly involved in the development of malformations (28).

Protection against infectious diseases such as rubella, avoidance of anesthesia, airplane trips, x-radiation and stress, and maintenance of a well-balanced diet during early pregnancy are protective measures deserving of careful evaluation and investigation.

Wound Healing

Chemical and histochemical methods of studying the healing wound have changed the total picture of the events occurring during repair. The classical description of repair is one of invasion of the wound by new capillaries and fibroblasts within 24 to 48 hr. after the injury. The sutured wound decreases in tensile strength during the first four to five days but regains full strength by about the fifteenth day when healing of the uncomplicated surgical incision is considered complete. During this period the number of capillaries diminishes, the fibroblasts increase, and reticulum and collagen fibers are deposited (29). The technique of determining the progress of healing by the tensile strength of the healing tissue has been used in studies of skin (30), tendon (31), and hollow viscera.

Sandblom (32) has reported that remote but symmetrical experimental secondary wounds heal more rapidly than the primary wound. A specific growth-promoting substance acting systemically and released between the first and fourth week after the injury was postulated. This often-quoted observation was later proven invalid by Sandblom himself who discovered that the effect was due to technical errors related to the depilation of the animal (33). Clipping of the hair temporarily decreases healing capacity. No difference in tensile strength was noted in primary and secondary wounds when depilation immediately preceded each incision. It must be concluded that the wound stimulus is local. It may be altered by general nutritional deficiencies, such as protein (34) and vitamin (35), and by cortisone administration (36, 37).

The role of the epidermis in wound healing has been studied in man and animals by Gillman *et al.* (38). The earliest microscopic evidence of wound activity is in the epidermis which rapidly migrates across the wound either

through or beneath the intervening clot. A fibrinolytic enzyme or other proteolytic enzyme is presumed to be formed by the epithelium enabling it to advance beneath the clot (39). Active cell mitosis appears at a distance from the incision and the thickened epidermis grows downward between the edges of the incision and also follows the path of each skin suture. Epithelium seals the wound before there is microscopic evidence of fibroblastic activity. The more slowly developing fibroblastic activity. is influenced by the intact epithelium. Progression to granulation tissue is arrested even in split skin graft donor sites because epithelial regeneration is so rapid. Only in absence of epithelial protection does the fibroblastic wound stimulus persist. The amount of contracture of the wound depends on a third factor, the presence of dermis. Billingham & Reynolds (40) have succeeded in separating dermis from epidermis. Experimental wounds covered by a graft of epidermis only, contract to about 25 per cent of their original size. Little contraction occurs if the graft comprises both dermis and epidermis.

More rapid healing of disrupted and resutured abdominal wounds is well-known. Savlov & Dunphy (41) have confirmed this observation in the experimental animal. The tensile strength of a standard abdominal wound was tested at three days. The wound was immediately resutured and tested again three days later. In all animals the tensile strength at the second test, three days after resuture, was at least three times as great as the first. Excision of the primary wound and resuture decreases but does not abolish the rehealing phenomenon. The rehealing effect reaches its maximum on the third day. The authors conclude that there are processes occurring in the wound which may be interrupted by the disruption but can resume promptly without the latent period characteristic of the primary wound.

Dunphy & Udupa (42) have followed these clues and applied newer chemical and histochemical techniques to an investigation of the events transpiring in the fresh wound. The authors have reviewed the current evidence of the formation of collagen—stating that it requires a substance probably generated by fibroblasts and a complicated mucopolysaccharide probably produced by mast cells or connective tissue cells, and that ascorbic acid and other enzyme substances are no doubt involved in the final deposition of adult collagen.

Two phases of healing are postulated by Dunphy & Udupa. The first or production phase is of the same duration as the "lag phase" but instead of being one of autolysis and phagocytosis only, it is marked by active preparation for final repair. Mucopolysaccharides, identified by special staining techniques, increase rapidly to a peak at five-to-six days. Reticular silver-staining fibers which also increase up to the sixth day are presumed to be evidence of the protein precursors of collagen. In the second phase the quantity of both polysaccharides and reticulum in the tissues decreases, as the collagen formed from them increases in the tissues. Simultaneously, the tensile strength of the wound increases.

In protein deficiency the production of mucopolysaccharides and

collagen is less and the time for production is longer. The amino acid methionine alone added to the diet will restore the rate of production toward the normal. Williamson & Fromm (43) have shown that the sulphur content of healing tissue is related to tensile strength. Dunphy *et al.* (44) have followed this evidence further by labeling the methionine with S^{35}. The uptake of S^{35} methionine in the wound is greater than S^{35} sodium sulfate uptake but the uptake of each is approximately equal in samples of cartilage from the same animal.

Dunphy and his colleagues report that the quantity of polysaccharides and reticulum in the wound remains high for as long as sixteen days in the ascorbic acid deficiency state. Collagen formation does not increase as it does in the controls. When ascorbic acid was given intramuscularly on the eighth day the tissue mucopolysaccharides fell rapidly and tissue collagen simultaneously appeared. The rapidity with which collagen increases in the tissues has led to the conclusion that the materials for collagen formation are present but that synthesis is delayed in the absence of ascorbic acid. Of immediate practical interest is the observation of Ye & Saffier (45) that the pH of the wound is a valuable and useful method of evaluating the condition of the wound. The measurement is made by color comparisons after pressing the strips of pH paper against the granulating surface. The higher the pH, 7.4 or above, the better its condition and the higher percentage of "take" of skin grafts used to close it.

Storage of Skin

The care of the local wound is today's critical problem in the severely burned (46). Fluid replacement, nutritional needs, and control of infection can be dealt with if complications in the wound can be minimized by clean care, debridement, and early closure. One of the most essential requirements for meeting the problem is adequate skin for grafting, skin which, in the extensively burned patient, may not be available. To have skin for these patients by the establishment of "skin banks" has been the concern of a number of investigators in recent years.

Living skin grafts can be preserved in a moist atmosphere at temperatures just above the freezing point. Autografting of such preserved skin has been successful after 35 days (47). Fresh homografts of skin whose life-saving usefulness has been demonstrated repeatedly may be preserved in the same way. The skin homograft which can serve only as a temporary cover may, at the critical time, be life-saving. The usual survival time of homografts is two weeks, but in the sick patient whose host resistance is reduced it may be prolonged.

Viable homografts of skin may be secured from living donors or from a suitable body within a few hours after death. The final death of cells of the skin does not occur at the same rate as death of cells of the nervous system. These homografts may be used at once or preserved as living homografts at 4°C. The medico-legal aspects of securing postmortem homo-

grafts and some of the moral aspects have been carefully summarized by Brown *et al* (48).

When skin is "banked" at +4°C. it will remain viable for about three weeks. This has been confirmed by successful autotransplantation (47), by animal transfer (49), by measurement of oxygen uptake (50) and enzymatic activity (51), and by tissue culture methods (52).

A nutrient medium containing dilute serum (10 per cent) and glucose is added to a balanced salt solution containing 50 units of penicillin and streptomycin per cubic centimeter. Skin stored in this mixture will survive longer than that stored in saline solution only. Exclusion of oxygen is detrimental to the graft. Phenol red which changes color as metabolites accumulate is a good indicator of the lowering pH and the need for a change of the preserving medium (54).

Storage of skin for an unlimited time is desirable if it is to be available for the emergency situation. This need has prompted studies of how best to prepare skin for "banking" at temperatures below freezing. There have been conflicting reports of the viability of skin stored at low temperatures but cell death appears to be related to the method of preparation. Clinically, whether viable or not, the skin homograft stored at below freezing temperatures is rejected sooner than the fresh graft, but its life-saving usefulness as a "skin dressing" may be just as great (54).

The hazard of freezing the skin graft is that ice crystals form. These may distort cell architecture, rupture cell membranes, precipitate protein, and concentrate salt as water is withdrawn. Such objections to freezing have been met in a number of ways.

Vitrification by very rapid cooling in liquid nitrogen (−196°C.) avoids crystallization and permits safe storage at —70°C. The warming process must be equally rapid because the crystallization during thawing is more damaging than that during cooling. Keeley, Gomez & Brown (53) failed to secure permanent survival of an experimental, rapidly frozen skin autograft in the dog whether immediately grafted or stored at 70°C.

Partial dehydration of the skin graft with glycol or glycerol prevents crystallization. The degree of dehydration depends on the duration of immersion of the tissue in the dehydrating solution. Keeley *et al.* (53) report a high rate of survival (98 per cent) of autografts of skin, dehydrated, rapidly cooled, rapidly warmed and immediately grafted. Following storage at 70°C. for 46 to 66 days, the rate of survival was 84 per cent. Other investigators have reported survival of skin grafts both in the experimental animal and in the human following partial dehydration and storage of the skin at a temperature near −70°C.

Freeze-drying or lyophilization will destroy the viability of the skin, but after moistening the dried graft looks like a fresh sheet of skin and will serve effectively as a wound covering. The graft is frozen and the ice evaporated under very low atmospheric pressure. After drying, the skin is stored in vacuum sealed tubes at room temperature (54).

From the above evidence it appears that prolonged "banking" of skin grafts for the emergency is feasible. The grafts will survive for several weeks in a nutrient medium at temperatures just above freezing. If partially dehydrated by immersion in glycerol or glycol, they can be frozen without being destroyed by the formation of ice crystals. These grafts retain viability, will "take" as fresh auto- or homografts, and, if the former, survive permanently. Dead skin (lyophilized) can be remoistened and used as an effective temporary wound covering despite its nonviability.

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DENTISTRY[1]

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The period since the last review (1) in 1954 is characterized by the completion of long-term studies on the control of dental caries in man and a continuing search for measures for the prevention of tooth decay. But although the present review is limited to problems of clinical importance in the etiology and control of dental caries, it should be emphasized that dental research is extending very rapidly and that important contributions have been made on tooth structure and composition, properties of the saliva, and oral pathology. Extensive surveys on experimental caries research (2), and on water fluoridation have been published (3).

Caries etiology.—Orland *et al.* (4) have demonstrated that no caries lesions developed in germ-free rats on a diet strongly cariogenic in control animals in ordinary environments. On the other hand germ-free animals monoinfected with enterococci showed dental decay (5). These findings, and the facts that a cariogenic diet did not produce caries when given by stomach tube (6) or in the left animal when given to the right in parabiosis experiments (7), provide part of the strongest evidence recently produced for the generally accepted chemoparasitic theory of the etiology of dental caries. Despite this, attempts have been made to produce new concepts of the caries-initiating process or to modify the older ones. Thus Schatz *et al.* (8, 9) have put forward the interesting theory that products of the proteolysis by the oral microflora act as chelating agents demineralizing the teeth at neutral pH. A consequence of this theory would be that acid-producing bacteria such as lactobacilli may act as anticarious factors. The theory of Schatz needs, however, confirmation by experimental evidence. According to Eggers-Lura (10), the conditions in the saliva of the susceptible individuals will favor the accumulation not of acids only but of compounds attacking the enamel at neutral pH by proteolysis and chelation.

Very interesting new tools in animal experimentation are the diets (11, 11a), producing also smooth surface lesions in rats where earlier diets almost exclusively produced occlusal cavities. According to McClure the incidence and severity of caries was significantly increased in the diets which contained skim milk powder that had undergone additional heat treatment by "dry autoclaving" (diet 636). Deficiency symptoms with growth failure occurred, however, and in subsequent experiments it was demonstrated that this might have been owing partly to lysine deficiency. McClure & Folk (12) showed that a supplement of 0.25 to 2.50 per cent *l*-lysine to the most

[1] The survey of the literature pertaining to this review was concluded in September, 1957.

caries-producing diet, diet 636, reduced caries by about two-thirds, D-lysine, *l*-arginine, or *l*-histidine did not inhibit caries produced by diet 636. Future work will show whether these diets provide not only a better scientific tool but also a new approach to the etiology of dental caries in man.

Caries bacteriology.—Although different strains of lactobacilli are widely accepted as important acid-formers in the dental plaque, and much work has been done to classify them (13, 14), other aciduric microorganisms such as streptococci have received much attention. The biochemical properties of 109 strains of oral micrococci have been established (15).

Utilization of glycosamine by the bacteria (16) suggests that salivary mucin may provide a source of amino acids and carbohydrate for oral microorganisms.

As there is a great need of caries-susceptibility tests (17), the relations between floras of caries-susceptible and caries-immune individuals have been studied. Green *et al.* (18) demonstrated that typical immune individuals have few or no lactobacilli in saliva or plaques. Krasse found (19) that the presence or absence of a correlation between caries activity and the number of lactobacilli appeared to be dependent on the degree of caries activity of the group studied. Caries activity was correlated with the number of streptococci in plaque material but not with that in saliva. There was, however, no relationship between caries activity and the incidence of *Streptococcus salivarius.*

Conditions favoring the development of the dental plaque are of pertinent importance in the investigation and control of caries. Mucinous polysaccharides formed by oral microorganisms have been suggested as one of the substances cementing the microorganisms together. Snyder *et al.* (20) found only two types capable of such a synthesis from sucrose. *S. salivarius* formed levan and a Gram-negative diplococcus produced amylopectin. However, as these compounds are water-soluble their importance as plaque-binders is unlikely. Using different strains of oral microorganisms either alone or in combination in the artificial mouth, Pigman *et al.* (21) were able to produce different types of lesions, ranging from those caused by lactobacilli, where the outer enamel surface was readily decalcified with only a slight action on dentinal matrix, to the other extremes using *Clostridium perfringens,* which destroyed calcified and decalcified dentinal matrix without any obvious signs of decalcification. The wide variety in the histological features of the carious lesions may thus be explained by the type or types of microorganisms present.

Caries and nutrition.—Reviews on sugar and dental caries have been published in 1953 by the Council on Dental Health of the American Dental Association (22), and in 1955 by Sognnaes (23) and Volker (24).

Two large-scale investigations on the relationship between carbohydrates and dental caries in man have been published. In the first (the Vipeholm study) caries activity was studied at an institution for five years in the

same 436 individuals with a mean age of 32 years (25). After a preparatory period during which the ten groups of patients had the same consumption of sugar at meals (90 gm. per individual and day), further sugar was added to the adequate basal diet *at* the meals in certain groups only, whereas in other groups some of the sugar added was given between meals also, in the form of candy. There was no increase in the low caries activity of the preparatory period even in those groups where the consumption at meals was as high as 330 gm. per person and day. In the candy groups, where sugar was consumed also between meals, there was a statistically significant increase in the caries activity of several times the figures of the preparatory period. After withdrawal of the candy the caries activity returned within the following year to the initial lower values.

In the study by King *et al.* (26) on 243 institutionalized children observed for two years, two subgroups were given 11 oz. and 22 oz. of sugar in the diet per week and individual. The candy or sweet consumption was not controlled, but the estimated amounts consumed were almost the same in both groups. Sometimes chocolates and sweets were given as part of a meal, sometimes immediately after, and sometimes between meals or even at bedtime. One must therefore assume that the sweets were consumed at random and equally so in both groups. The variable of importance was thus the increased consumption of sugar at meals. Since the caries experience was the same in both groups after two years, the result confirms the result of the Vipeholm study that a considerably increased consumption of sugar in the diet, i.e., at meals, has no influence on caries activity. The experimental conditions used in the study of King and his collaborators does not, however, warrant any conclusion on the influence of sugar consumed as candy or chocolate between meals.

These recent results agree well with the earlier studies in institutionalized children, where Jay *et al.* (27) demonstrated an increase of caries activity after consumption of large amounts of candy. Boyd (28) and Mack (29) did not find such an increase when sugar consumption at meals was increased as sugar or sweets. In accordance with the role of frequent consumption King (30) found no increase in caries when candy was given once a day at bedtime. The controlled clinical studies thus sustain the century-long experience of the dental profession that sugar consumption may increase caries activity in susceptible individuals. It is then the form, composition, or manner and frequency of consumption more than the amount of sugar that is of importance.

In a study of food habits in school children and dental caries by Potgieter *et al.* (31), however, only a slight positive relationship was noted between caries experience and frequency of between-meal snacks, or total consumption of candy and soft drinks. According to Savara & Suher (32) there was no association between dental caries in school children and the number of times per week candy was consumed, the frequency of food con-

sumed between meals, or the number of times a day the child brushed his teeth. Studies of this type are, however, fraught with the difficulty of obtaining reliable data on the sugar consumption and food habits.

Restriction of carbohydrates is still an important measure in the treatment of rampant caries (33, 34, 35). In this connection it has become important to classify foodstuffs according to their caries-producing capacities either by measuring the persistence of sugar in the mouth, the acid produced in the plaque or saliva, or the amount of food adhering to the teeth after ingestion. A comprehensive review of these studies has been made by Bibby (36), and here reference will be made only to the recent papers by Ludwig & Bibby (37, 38). Swenander Lanke (39) found greater variation in sugar persistence in the mouth among different individuals than among different foodstuffs tested in the same person. It was also demonstrated that if an individual had a short clearance time for one foodstuff, it was short for other foodstuff, too.

The complexity of the relationship between nutrition and caries is stressed further by the fact that the cariogenicity of diets in animal experiments may be decreased by cooking the diet (40), or by adding fats (41) or ash from natural diet (42, 43). The latter effect might be exerted by trace elements, and it has been demonstrated that vanadium (44, 45, 46), beryllium (47), and molybdenum (48, 49) considerably decrease the effect of cariogenic diets in animals. Increasing the phosphate content also had a decreasing effect in animal experiments (50) of up to 90 per cent (51).

Caries prevention.—The year 1955 marks the completion of ten-years experience in three of the main studies on water fluoridation. In Grand Rapids (52) the reduction of dental caries was about 60 per cent in children born since fluoridation. Some reduction also occurred among children born prior to fluoridation. Only milder forms of fluorosis occurred and the incidence increased very little during the ten-year period (from 0.24 per cent to 0.36 per cent of the children). The caries reduction in Brantford (53) was of the same magnitude as in Grand Rapids. In the third study in Newburgh (54) the reduction in the six- to nine-year-old children was 58 per cent compared with children of the same age in the nonfluoridated control city of Kingston. Also in this study there was a considerable reduction, 40 to 50 per cent, in the older children who were born prior to fluoridation. Disfiguring mottled enamel was not found in the Newburgh children. In the Evanston study (55) there was a 58 per cent reduction of dental caries after seven years of fluoridation.

Excellent reviews on the metabolism and systemic effects of fluorides have recently been published by Cox (56), Hodge & Smith (57), Largent (58), and Hodge (59), all stressing the safety of water fluoridation. Extensive studies in connection with the fluoridation projects have failed to show any harmful effect of the added fluorides. Thus, Schlesinger *et al.* (60) found no differences of medical significance between 500 children in Newburgh with fluoridated water and 405 children in the control city. The

examinations included general medical examination, height and weight measurements, roentgenograms of hands, knees and lumbar spine, hemoglobin levels, and total leukocyte counts. In smaller groups of children careful examination was made of vision and hearing and detailed urinary analyses were performed. The death rates from cancer and cardiovascular-renal diseases were of the same magnitude in Newburgh and Kingston. They were lower in Newburgh with fluoridation in seven out of the ten years for cancer and lower in Newburgh in five out of the ten years for cardiovascular-renal diseases.

In order to institute caries prevention by fluorides in populations without communal water supplies, or for other reasons, topical application of fluorides or administration of fluorides in tablets (61, 62, 63) has been used. The topical application of sodium fluoride gave the generally attained reduction of 30 to 40 per cent in deciduous teeth (64), but the earlier negative results in adults have been confirmed (65, 66). In accordance with the study of Schützmannsky (67), Syrrist (68) found no statistically significant reduction during the post-treatment period of five years; nor was any acceleration of the caries attack in the treated teeth demonstrable.

Cohen & Massler (69) and Peterson & Jordan (70) found that the topical application of sodium silicofluoride was not more effective than sodium fluoride. Using 2 per cent stannous fluoride Howell *et al.* (71) achieved a better result than with sodium fluoride. Slack (72), however, found some caries reduction with stannous fluoride, but considerably less than did Howell. The reduction by stannous fluoride in the study by McLaren & Brown (73) was 46 per cent.

The first reports on the benefits of an unsupervised use of a dentifrice containing stannous fluoride by Muhler and his associates (74, 75) were very encouraging with a reduction of about 50 per cent in tooth decay both in children and adults. Jordan & Peterson (76) found a smaller reduction of about 35 per cent in school children. That the other constituents of the tooth paste are of decisive importance in studies of this type was demonstrated in a recent paper by Muhler (77), who found no reduction with a tooth paste containing stannous fluoride and dicalciumphosphate as the polishing agent.

With regard to dentifrices medicated with antienzymes, a survey of which was given by Fosdick (78), the interest is at present centered about those containing sodium lauroyl sarcosinate. Its effect has been studied in adults by Fosdick (79) with the promising results of about 50 per cent reduction in dental caries after two years unsupervised brushing with a dentifrice containing two per cent sodium lauroyl sarcosinate. Using this compound in rat studies, Zipkin & McClure (80) demonstrated a statistically significant reduction of about 60 per cent in dental caries. Volker *et al.* (81), however, found only a small effect of sodium lauroyl sarcosinate against hamster caries.

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LABORATORY AIDS TO DIAGNOSIS AND THERAPY (PAPER CHROMATOGRAPHY AND ELECTROPHORESIS)[1]

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So many papers have appeared in the last two years describing the application of paper chromatographic and electrophoretic techniques in the clinical laboratory that even a simple bibliography is not possible in the space available. The application of paper electrophoresis, particularly in its clinical aspect, has expanded at a remarkable rate since its use in the study of serum and plasma proteins was first described in 1949 (45). Since then the technique has been applied to the study of virtually every body fluid and many other tissues in both physiological and pathological states.

In general, there appears to be a tendency to apply paper electrophoresis to studies involving proteins, while paper chromatography is usually favored for studies of the smaller metabolites such as nonprotein nitrogen (NPN), steroids, etc. Exceptions to this are exemplified by the application of chromatographic techniques to the separation of hemoglobins (91) and the use of cellulose ion exchange chromatography for serum proteins (201). Another exception is the application of high voltage techniques to amino acid and NPN constituents where truly remarkable resolution has been attained. [See paper by Kickhöfen (225) for summary.]

Serum proteins continue to be the most popular subject for study by paper electrophoresis, and examples are too numerous to mention as such. The various hemoglobinopathies are the subject of perhaps the category next most frequently studied with almost equal interest shown in urinary proteins and proteins of the cerebrospinal fluid (after concentration by ultrafiltration or concentration dialysis).

The protein moiety continues to be the main interest in serum studies. Next, lipoprotein studies appear to be receiving the most attention. Determination of the glycoproteins from a quantitative standpoint leaves much to be desired because of the poor reproducibility associated with the poor stability of the colored bands produced by periodic-Schiff reagents. A genuine need exists for better glycoprotein determination techniques. Studies describing the simultaneous application of all three detection techniques to the same serum sample have been described (230).

Examples of individual papers concerned with less frequently studied clinical substrates are: amniotic fluid (39); aqueous humor (228); bile (218); blood (cord), (64); brain tissue (105); cantharides blister fluid

[1] The survey of the literature pertaining to this review was concluded in January, 1957.

(2, 95, 231); cerebrospinal fluid (34, 36, 120, 173, 174, 177, 179, 206); crystalline lens (13, 144, 164); cyst contents (56); dental pulp (212); endolymph and perilymph (100, 221); exudates and transudates (55, 110, 176, 229); gastric juice (81, 82, 123, 142, 151, 188); lymph (147); milk (193, 234); nerve proteins (109); perspiration (216); prostatic fluid (152); protein-bound components of liver and brain (33); miscellaneous tissues (32, 41, 115, 164, 169, 202, 221); thyroid extracts (46, 90); tumor extracts (85); saliva (113); semen (22, 23, 24, 132, 152, 189, 194, 198); skin proteins (203); serum-species studies (3, 4, 7, 26, 48, 69, 119, 146, 197); tears (138, 139, 143); urine (51, 77, 134, 155, 161, 192, 198a, 208, 211, 226).

Recent studies on large cross-sections of hospital admissions have appeared (99, 209) as well as a monograph on clinical applications of paper electrophoresis (42). A series of symposia on paper electrophoresis have been held recently, all well-represented from the clinical viewpoint (148, 149, 150, 225). Many papers have been published recently dealing with specific diseases or physiological states. The following were selected for mention here: agammaglobulinemia (78, 219); alcoholism (124); alimentary lipemia (83); amyloidosis (11, 127, 197); anemia (160); anemia (sickle cell) (65, 91, 93, 126, 190, 191); arthritis (121a, 133); atherosclerosis (47, 67, 98, 178, 222); carcinomatosis (5, 68, 92, 102, 157, 181, 217); cryoglobulinemias (15); diabetes mellitus (1, 51, 52, 53, 62, 107, 108, 187, 196); diet (112); dystrophy and toxicosis (25a); electrotrauma (14, 94); erythroblastosis fetalis (215); exercise (79); fever (40); fractures (106); galactosemia (172); geriatrics (130, 157); heart disease (congenital), (74); hereditary hemolytic disease (213); infectious diseases (103); infections with *Miyagawanella psittacii* (71); infections with *Plasmodium berghei* (31); kala-azar (6); keratoconjunctivitis sicca (139); kidney disease (30, 77, 87, 88, 185, 198a, 207, 211); leprosy (135); leukemia (76, 181); liver disease (17, 44, 60, 73, 114, 185a, 186, 224); lupus erythematosus (95); macroglobulinemia (158); measles (89); myocardial infarction (43, 98, 99, 107, 166); myopathies (145); multiple myeloma (16, 19, 20, 29, 59, 155, 162, 170, 183, 184, 195, 199); multiple sclerosis (173, 175, 223); nephropathies (96, 198a); nephrotic syndrome (77, 88, 198a, 207, 208); normal studies (35, 57, 99, 101, 111, 131, 171, 178, 204, 209); panmyelopathies (128); parasitic diseases (205); poliomyelitis (177); pregnancy (18, 49, 154, 159, 182, 233); proteinemias (195); radiation effects (84, 86, 217); rheumatic conditions (37, 61, 72, 116, 121, 121a, 165, 210); rheumatoid arthritis (63, 92a, 121a, 214); shock (hemorrhagic) (122a); skin diseases (25, 129); surgery (156, 163); syphilis (rabbit), (118); thyroid studies (38, 46, 70, 122); thalassemia (65, 147b); typhoid (rabbit) (21); tuberculosis (meningitis) (12, 104); tuberculosis (pulmonary) (34, 50, 54, 141, 232); venous thrombosis, experimental (167); and virus diseases (66, 88, 177, 185a).

Examples of papers dealing with the correlation of paper electrophoretic findings with other diagnostic tests are: chemical protein determination (153); Coombs test (80); De La Huerga-Popper reaction (28); diazo-positive substances (75); Jaffe reaction (75); Kunkel-Ahrens-phenol re-

action (8, 27); Middlebrook-Dubos test (180); and Vernes reaction (180).

Recent clinical reviews of paper electrophoresis are: (19, 57, 93, 117, 130, 168, 187, 195). A number of reviews and books have appeared in which details of techniques are stressed (9, 10, 42, 125, 137, 147a, 225, 227). Other interesting new developments are (*a*) the starch-gel electrophoretic technique of Smithies (200) which appears to combine a sorting process dependent upon molecular size with electrophoretic mobility, and to afford much higher resolution than is available with simple paper techniques. (*b*) The cellulose ion-exchange chromatographic method of Sober & Petersen (201) appears to afford the highest resolution of any single technique yet described for serum proteins. Unfortunately, in its present form, it is not convenient for routine clinical application. It seems likely, however, that this principle will eventually be applied to routine analysis in the clinical laboratory. (*c*) The immuno-electrophoretic technique of Grabar & Williams (19, 20, 69a, 224a), is being used increasingly in clinical studies and as a criterion of homogeneity for protein fractions.

A large amount of information is beginning to accumulate. It is unfortunate that there exists no general agreement concerning detailed techniques. Many papers continue to appear which seek to establish normal values and explore numerical relationships which are based on uncritical or even incomplete evaluations of the multiple steps involved. Thus, much published data are not subject to quantitative comparison. Paper electrophoresis in particular involves so many steps that some agreement as to detailed procedure must come before the technique can be utilized to its full potential as a diagnostic tool. A recent symposium was devoted to this thesis and the volume reporting its results is indicative of the many points of view (225).

Several papers have appeared recently attempting to evaluate and analyze critically the factors involved in the quantitative application of electrophoresis; typical examples are—9, 10, 32a, 59a, 70a, 97, 97a.

In this reviewer's opinion, the most straightforward method for the evaluation of paper patterns is simple elution and reporting the amount of a standard dye bound for the mobility species in question without regard to artificial "dye binding factors," etc. This requires no assumptions except that the dyeing technique results in a stoichiometric protein-dye relationship, and makes it immaterial whether the numerical values are obtained by elution or by direct scanning (providing, of course, the scanner employed is calibrated to give the same values as would be obtained if the dye were actually eluted). In essence, this approach makes a relatively simple dye of known chemical structure. The common denominator for comparison and definition does not require a detailed knowledge of the composition of the proteins making up any given mobility class, as would be the case if a "standard protein" were to be employed.

The subject is complicated and extensive discussion is beyond the scope of this review. These questions are considered in detail by the author and others in reference (225).

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LABORATORY AIDS TO DIAGNOSIS AND THERAPY (ENZYMES)[1,2]

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Pepsinogen and uropepsin.—Normal plasma contains significant quantities of pepsinogen which are presumably of gastric origin. In a series of patients with duodenal ulcer or gastric ulcer the plasma pepsinogen levels were found to be greatly elevated [Mirsky *et al.* (1)], whereas after subtotal gastrectomy as well as in the presence of carcinoma of the stomach low values were observed. Among a large group of patients with pernicious anemia, the mean plasma value was also low. A low plasma pepsinogen level in the presence of gastric ulceration is a strong indication of cancer but pernicious anemia must be excluded. After a satisfactory vagotomy a fall in plasma pepsinogen can be expected.

A proteolytic enzyme can also be detected in urine. This enzyme, usually termed uropepsin, is believed to originate like gastric pepsin from pepsinogen secreted by the gastric glands. However, in the case of uropepsin, the enzyme is secreted directly into the blood and then excreted into the urine. Peak *et al.* (2) have suggested a simpler method for the determination of uropepsin than the tyrosine method of Anson and Mirsky which has most frequently been used. These authors have found that measurement of uropepsin is of value in the diagnosis of gastrointestinal diseases, notably peptic ulcer and gastric carcinoma. In those macrocytic anemias which are associated with an achlorhydria which is not altered by stimulation with histamine, it is a reliable differential test to exclude pernicious anemia. In cases of massive hematemesis uropepsin values are useful in differential diagnosis; low levels consistently occur when bleeding is from esophageal varices, whereas high values are the rule when bleeding is due to a duodenal ulcer. There appears to be a relationship between the activity of the adrenal cortex and uropepsin. A decrease is noted in patients with panhypopituitarism or Addison's disease, but a definite increase occurs in Cushing's disease and is accompanied by parallel alterations in corticoid and ketosteroid excretion. Attention to the uropepsin excretion may be a valuable means of anticipating gastrointestinal complications attendant upon long-term hormonal therapy.

Amylase.—The amylase normally present in the blood is derived not

[1] This review was prepared from literature available to the author up to July 1, 1957.

[2] The following abbreviations are used in this chapter: CE (cholinesterase); LDH (lactic dehydrogenase); MDH (malic dehydrogenase); SG-OT (serum glutamic-oxaloacetic transaminase); and SG-PT (serum glutamic pyruvic transaminase).

only from the pancreas but also from the salivary glands and liver [Popper & Necheles (3)]. Elevations of the serum amylase may occur during the first 72 hr. after an attack of acute pancreatitis. In milder inflammations small rises which are noted for only a few hours may be characteristic; hence it is necessary to perform early and frequent determinations in such cases. A rapid drop to normal may indicate early resolution of the inflammatory process, but similar findings result when destruction of the pancreas is so excessive that cessation of production of enzymes has occurred. It is therefore not possible to correlate the severity of the disease with the degree of elevation of the serum amylase [Dreiling & Janowitz (4)]. A normal amylase level does not exclude a diagnosis of disease of the pancreas and, conversely, serum amylase may be elevated in a number of situations in which no disease of the pancreas can be demonstrated. These latter include acute disease of the gallbladder (5), perforated peptic ulcer (6), uremia (7), after cholangiography (8), and after administration of morphine-like narcotics and parasympatheticomimetic drugs (9). Provocative tests have been developed in an effort to improve the diagnostic value of blood enzyme studies particularly in chronic pancreatitis. However, Dreiling & Richman (10) concluded that these tests point to the possibility of diseases of the pancreas when positive but are not dependable for diagnostic purposes.

Amylase is freely excreted by the kidney and the amount excreted in a given time may reflect the total amount secreted by the pancreas into the blood. Saxon *et al.* (11) report that urine amylase is always abnormally high when the serum amylase is high, if renal function is adequate; furthermore, urine amylase remains abnormal as a rule 7 to 10 days after the serum concentration has returned to normal. This may render urine determinations more useful in diagnosis when the patient is not examined within the first few days after the onset of the attack or when the attack is mild. A 2-hr. collection of urine was found adequate. In one patient with a pancreatic cyst containing over 25,000 units amylase/100 ml., the daily urine excretion remained abnormal at least 6 weeks after the serum concentration had returned to normal. The urinary amylase excretion reflected the clinical course of the patient much more adequately than did the serum.

Lipase.—Increases in serum lipase tend to parallel those of amylase in acute pancreatitis but lipase increases occur later and tend to persist longer. Determination of lipase may be useful when abdominal pain occurs in conjunction with mumps; serum amylase may be elevated because of involvement of the salivary glands, but unless lipase is also elevated a complicating pancreatitis may be ruled out [Warren (12)]. Some commonly used methods for determination of serum lipolytic activity do not distinguish between so-called esterase activity (pseudocholinesterase) and lipase of pancreatic origin. Henry, Sobel & Berkman (13) report that the method of Cherry & Crandall (14) which uses olive oil as substrate specifically measures

lipolytic activity of pancreatic origin. Increases in these lipase values may also occur in carcinoma of the pancreas and in hepatic disease.

Trypsin.—Elevations of trypsin in the serum presumably occur during acute disease of the pancreas with resultant changes in the coagulability of the blood; indeed, according to Innerfield *et al.* (15), the plasma antithrombin titer depends directly upon the rate of release of trypsin into the bloodstream. Reports on the clinical use of plasma antithrombin titer in pancreatic disease include those of Innerfield (16) and of Dreiling *et al.* (17).

Cholinesterases.—A number of tissues exhibit cholinesterase (CE) activity. Vorhaus & Kark (18) have reviewed the clinical significance of serum CE. In general, low levels are found in patients ill with liver disease, malnutrition, chronic debilitating and acute infectious diseases, and anemias. Normal levels are found in patients with uncomplicated obstructive jaundice, myasthenia gravis, hyperthyroidism, and many other diseases. High levels occur in the nephrotic syndrome. Serum CE is apparently produced only by the liver and in parallel with albumin; its synthesis seems to be stimulated or inhibited by factors which similarly affect albumin production. A large number of drugs produce a temporary decrease in CE activity. However, the alkyl fluorophosphates, particularly diisopropylfluorophosphate, cause irreversible inhibition of the enzyme. Some insecticides in common use depress CE and tests for CE activity may be used to detect over-exposure to these agents.

Sabine (19) has pointed out that there is more cholinesterase in human red blood cells than in the serum. She has devised a simple colorimetric method for routine clinical use in determining red cell CE. The determination can be made on whole blood by adding quinidine which inhibits selectively the CE activity of the serum (20). The CE titer of erythrocytes in the peripheral blood seems to be a sensitive indicator of hematopoietic activity—perhaps more so than the reticulocyte count, according to Scudamore *et al.* (21). Studies of red cell CE in various anemias indicate that it is low in untreated pernicious anemia or in hypoplastic anemia; it is high in patients with anemia secondary to hemorrhage or the anemia of nontropical sprue in early remission. Sabine (22) believes that the activity of red cell CE can be used as a test of bone marrow function in anemic states and as a means to gauge response to therapy or the onset of a relapse.

Alkaline phosphatase.—The majority of adults with a very high serum alkaline phosphatase have Paget's disease, metastatic carcinoma, or biliary obstruction. However, Ross *et al.* (23) have pointed out that elevations in alkaline phosphatase may occur in the absence of jaundice in patients with chronic infiltrative disease of the liver due, for example, to sarcoid, tuberculosis, or Hodgkin's disease. This is not usually seen in cases of extrahepatic biliary obstruction and the observation may therefore be of value in differential diagnosis. Gibbons (24) states that the presence or absence of either hepatic metastases or of common bile duct pathology in anicteric

patients can be predicted with a high degree of accuracy by determination of alkaline phosphatase. If elevated levels are obtained before a cholecystectomy, it is a warning that exploration of the common duct and drainage will probably be required. In patients with cancer, elevated alkaline phosphatase suggests metastic spread to the liver, and when used preoperatively it indicates how extensive the surgical procedure must be. It is useful as a screening test for neoplasia, and, at times, it is the only clue to the presence of an occult neoplasm such as carcinoma of the body of the pancreas.

Acid phosphatase.—The determination of the activity of serum acid phosphatase has its greatest clinical value in studies of patients with carcinoma of the prostate, particularly to detect the occurrence of metastases as well as to assess the progress of therapy in such cases. However, human serum contains a number of different acid phosphatases derived from different types of cells. Consequently, attempts have been made to render the determinations more specific for acid phosphatase of prostatic origin. Reynolds *et al.* (25), using copper to inhibit erythrocyte acid phosphatase, found that a high percentage of patients with widespread cancers of the female breast or of the prostate gland had significantly elevated values for copper-resistant acid phosphatase. Fishman *et al.* (26) reported on their generally favorable experience using the method of Fishman & Lerner (27) in which an effort is made to differentiate serum acid phosphatase of prostatic origin by comparison of the activity obtained with or without the addition of L-tartrate to inhibit "prostatic" acid phosphatase. Bensley *et al.* (28), in a study of 375 patients, found that tartrate inactivation of more than one unit/100 ml. lends support to the diagnosis of carcinoma of the prostate. However, 54 proven cases of prostatic carcinoma had tartrate-inactivated activity of one unit/ml. or less, a value which also occurs in a variety of nonprostatic diseases and hence is not diagnostically significant. Hill (29) was unable to demonstrate any improvement by use of the tartrate technique over measurement of total acid phosphatase if the carcinoma is apparently still localized. Bonner *et al.* (30) suggest that when there is a questionable diagnosis of prostatic cancer the administration of testosterone (in three 50 mg. doses during a one-week interval) may be followed by a significant rise in "prostatic" (tartrate-sensitive) acid phosphatase by stimulation of the growth of the tumor.

Serum copper oxidase.—The majority of the copper in the serum does not react directly with sodium diethyldithiocarbamate, the reagent used for colorimetric measurement of copper. This "indirect-reacting" copper is bound to an α-globulin (ceruloplasmin) and the copper-globulin complex has been shown to be an enzyme which exhibits oxidase activity, most active with *p*-phenylenediamine as a substrate (31, 32). Markowitz *et al.* (33) studied copper, ceruloplasmin, and oxidase activity in sera from normal human subjects, pregnant women, and patients with infections, hepatolenticular degeneration (Wilson's disease), and the nephrotic syndrome. Copper oxidase activity was increased in pregnancy and infections. In

Wilson's disease serum copper was low, particularly that of the ceruloplasmin fraction because of the hereditary ceruloplasmin deficiency which is characteristic of this disease. As a result, copper oxidase activity is also much reduced. In other neurologic diseases there is no change in the total serum copper or in ceruloplasmin. Copper oxidase is occasionally low also in nephrosis possibly because of losses of ceruloplasmin in the urine. Thus, abnormally low serum copper oxidase activity is strongly indicative of Wilson's disease. Ravin (34) has described a very simple and rapid colorimetric test to be applied to serum for measurement of copper oxidase activity. He suggests that use of this test in cases of obscure liver or brain dysfunction may lead to earlier detection of hepatolenticular degeneration and, therefore, to more effective therapy.

Transaminases.—The reversible transfers of amino groups between α-amino acids and α-keto acids are catalyzed by enzymes which are designated transaminases. There are a number of such enzymes which can be identified in most of the tissues of the body. An example is glutamic-oxaloacetic transaminase (G-OT) which is present in all tissues except bone. It is found in highest concentration in heart muscle, with skeletal muscle, brain, liver, kidneys, testes, and lungs following in order of decreasing concentration. The activity of G-OT in the serum is normally very low (5 to 40 units/ml.). However, levels rise in the serum when the enzyme escapes from injured cells and thus gains access to the blood (35). Determination of SG-OT is therefore now widely used to aid in the diagnosis of myocardial infarction. Agress *et al.* (36) experimentally produced graded myocardial infarctions in dogs and found good correlation between the amount of the infarct as estimated at autopsy and the peak SG-OT levels which occurred 9 to 23 hr. after production of the injury. Rudolph *et al.* (37), after experimental production of infarcts of kidney, spleen, heart, lungs, and intestines by ligation of the arterial supply to the organs, detected a rise in SG-OT in proportion to the degree of necrotic changes produced. Ischemia of short duration produced no increase in enzymatic activity. These and other authors emphasize that increased SG-OT activity is a manifestation of tissue damage but not specifically that of heart or liver. However, the relatively high transaminase content of these two organs makes it likely that either or both are involved when SG-OT is significantly elevated, unless there is also extensive trauma of skeletal muscle. Chinsky *et al.* (38) reported SG-OT studies on 400 patients of whom 117 had acute myocardial infarctions. SG-OT was increased in 114 with only 4 false negatives. The levels of the enzyme usually became significantly elevated about 6 hr. after onset of chest pain, rose to a peak at about 24 hr. and then returned gradually toward normal which was reached on the 3rd to the 6th day.

SG-OT is elevated in neurologic diseases which destroy skeletal muscle. The greatest increase is seen in the acute stage of dermatomyositis and the elevated levels may persist for several weeks (39). Green *et al.* (40) found

highly significant G-OT activity in the spinal fluid from 7 of 11 patients with clinical cerebral infarctions although the serum levels remained normal. These authors suggest that determination of spinal fluid transaminase may help to differentiate cerebral infarctions from other neurologic disease.

Increase in SG-OT may also serve as an indicator of acute hepatocellular damage. In hepatitis, not only are very high levels found during the first week of the illness, but the rise may actually precede the appearance of jaundice by 1 to 4 weeks thus permitting diagnosis in exposed subjects during the preicteric or prodromal stage (41). The extent of the rise in SG-OT in cirrhosis is dependent on the amount of active hepatocellular damage (42).

The clinical applicability of serum transaminase determinations has recently been summarized by Conrad (43), Ticktin, Ostrow & Evans (44), and Chinsky & Sherry (45).

The activity of glutamic-pyruvic transaminase (G-PT) is relatively greater in liver than in other tissues when compared to G-OT. Wróblewski & La Due (46) suggest that measurement of SG-PT may therefore be more sensitive than SG-OT in detecting acute hepatocellular damage; furthermore, SG-PT is not appreciably altered by acute cardiac necrosis.

Lactic dehydrogenase.—After myocardial infarctions lactic dehydrogenase (LDH), which occurs in high concentration in heart muscle, is found to be elevated in the serum (47, 48). LDH is not increased in those diseases which enter into the differential diagnosis of acute myocardial infarction: pulmonary embolism, pericarditis, severe angina, or acute cholecystitis. White (49) compared the diagnostic value of SG-OT and LDH in a number of patients with myocardial infarction. He concluded that LDH is superior not only because it is simpler to assay but also because of the greater degree and longer duration of its increase in the serum. Hsieh & Blumenthal (50) have reported on LDH activity in a number of disease states. As is the case with SG-OT, any cause of tissue destruction may elevate LDH.

Other enzymes.—The activities in the serum of several other enzymes of intracellular origin have also been reported. The diagnostic value of malic dehydrogenase (MDH) and of phosphohexose isomerase in patients with myocardial infarction or with liver disease has been evaluated by Bing, Castellanos & Siegel (51). Results in myocardial infarction were similar to those observed with G-OT. However, it was suggested there may be less overlapping with MDH or isomerase than with G-OT when patients with liver or myocardial disease are compared. Bodansky (52, 53) has reported that isomerase activity is increased in the presence of certain metastatic tumors, and that there appears to be a correlation between elevation in the activity of this enzyme and the growth of metastatic tumors.

The serum aldolase activity in patients with acute hepatitis is increased; a very minor increase occurs in cirrhosis, latent hepatitis, or biliary ob-

struction [Cook & Dounce (54); Bruns & Puls (55)]. Aronson & Volk (56) studied serum aldolase in neuromuscular disorders. Definite elevations were found in progressive muscular dystrophy, particularly in the childhood form of the disease. Levels were normal in cases of diffuse vascular or degenerative cerebral disorders even with extensive muscle atrophy, as well as in muscle wasting of nonneurologic origin.

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SOVIET MEDICAL RESEARCH: SOME RECENT ADVANCES AND FUTURE PLANS

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Since the end of World War II and until 1956, scientific contacts between the United States and USSR were so limited that the vast Soviet medical and biological literature was largely neglected. With re-establishment of exchange of scientific missions between the two countries it became apparent that, through the years, the Soviets have made full use of our published reports and assured dissemination of foreign and domestic scientific information through such special channels as the All-Union Institute of Scientific and Technical Information. In contrast, little use was made by our professions of the few Russian journals received and the knowledge of Soviet developments was less than sketchy. To correct this situation in 1956, the U. S. Senate appropriated special funds to support several government agencies in the task of organizing an unprecedented campaign for translating, abstracting, and reviewing the published Soviet scientific output to be placed at the disposal of our research workers in medical and related fields.

The immensity of this task is realized when some of the facts and figures are taken into account. A recent reviewer (1), concerned primarily with chemical literature, examined 715 available Soviet scientific and technical periodical publications. In his analysis the largest single group of 120 periodicals (16.8 per cent) was devoted to medicine with an additional 51 publications (7.1 per cent) dealing with biology. In addition to these counted 171 titles, numerous serial publications are in existence, such as *Uspekhi* (*Advances*) which is devoted to reviews of specific specialties and subspecialties of medicine. This list, of course, did not include the many independent journals published by the other Eastern European countries.

Some aspects of the approach developed by the responsible United States agencies were summarized by O'Dette (2) and Adams (3). In brief, it consists of initiating and supporting reviews of published papers in the major fields, of abstracting all the available biomedical literature, of translating Soviet-prepared abstracts of their own current articles, and translating selected monographs and individual papers of crucial importance to an understanding of the background of Soviet research and clinical concepts.

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Finally, a most ambitious undertaking is the support for regular cover-to-cover translation of several important Russian journals. At present, eight Soviet journals are thus available in English, namely, *Biochemistry, Bulletin of Experimental Biology and Medicine, Biophysics, Journal of Microbiology, Epidemiology, and Immunobiology, Problems of Oncology, Problems of Virology, Sechenov Physiological Journal of the USSR,* and *Problems of Hematology and Blood Transfusion.*[2] These translated journals are distributed, in support of grant and independent research, to 400 medical libraries in the tax-supported or nonprofit category, or both, and are available to others from the publishers at modest subscription rates. Obviously, the initial endeavor represents only certain facets of the broad field of biomedical research, and the clinical aspects of the disciplines are not yet adequately covered. To some extent these gaps are filled by extensive new abstract services in English provided by *Excerpta Medica* and *International Abstracts of Biological Sciences* and the greatly expanded coverage of Soviet literature by both *Biological Abstracts* and *Chemical Abstracts. International Abstracts of Biological Sciences* is a new journal which devotes considerable space to Russian articles, while *Excerpta Medica* now issues a separate periodical journal entitled *Abstracts of Soviet Medicine.*

The vigorous activities on the part of Western scientific circles are eagerly supplemented by apparent efforts of the Russian journals to bring their contents to the attention of non-Soviet readers. A number of Soviet journals in 1957 resumed or initiated the practice of including English language abstracts at the end of each original paper as well as a translated table of contents in parallel with the Russian. The Soviet scientists' expressions of willingness and desire to exchange scientific information have been noted by many of the recent medical travelers to Russia. A well-annotated list of references to available first-hand reports on Russian medical research and personalities by Western visitors was recently compiled and is particularly useful in evaluating Soviet literature (4). An interesting study on *The Use of Soviet Medical Research Information by American Medical Scientists* (7) was recently published. It is a useful inquiry into the current attitudes of our research workers and factors determining their utilization of the available journals.

The broad scope of Soviet medical research represents the combined productivity of numerous institutes (estimated to number about 500), clinics, and laboratories and generally is not unlike that of the United States or any other large and productive country. An interesting document providing a glimpse into the hopeful future plans of the Soviets is available for outside inspection. This is the "Research Plan of the Academy of Medical Sciences USSR, 1956-60," presented and accepted as part of the sixth overall five-year plan at the 20th Congress of the Communist party of the Soviet Union held in Moscow in February, 1956. It was briefly but lucidly reviewed

[2] The first two are published by the Consultants Bureau, New York, and the remaining six by the Pergamon Press of New York and London.

by Paul (5), following his return from Russia as a member of an official U. S. medical mission.

The detailed plan emphasizes the need for further investigations in 22 specified fields and includes under each topic not only a brief review of its over-all status but lists the particular problems requiring immediate attention and even suggests the possible means of experimental approach by the responsible Institutes. Some idea of its scope may be gained from a condensed outline of the main headings and some of the specific problems mentioned.

1. *Physiology and pathology of higher nervous activity* (in man and animals, including ontogenesis, development, aging, and prevention of disease).

2. *Basic mechanisms of activity of the nervous system and their role in regulating the bodily functions* (physiology and pathophysiology of corticovisceral interrelations; regulation of blood circulation, respiration, and digestion in normal and pathological states).

3. *Mechanisms of regulation of metabolism, the functions of proteins and their structure* (regulation of metabolism in physiological and pathological states and its development in ontogenesis and phylogenesis; regulation of enzyme activity; properties, functions, and amino acid composition of individual proteins; transformation and synthesis of proteins within and outside the body).

4. *Mechanism of action of pharmacological substances and search for new compounds* (relation between chemical structure and pharmacological effect; mechanisms of drug action; production of new drugs).

5. *Morphology* (structural evolution of the brain; mechanisms of innervation and their role in the regulation of physiological and pathological processes; growth and development of cells, noncellular structures, and tissues; pathology of cardiovascular system, of fibrous structures, of radiation injury, of infectious and immunologic processes, of occupational diseases; pathological growth and tumors).

6. *Principles of the prophylaxis and treatment of hypertensive disease, arteriosclerosis, and coronary insufficiency* (etiology, pathogenesis, clinical aspects, prevention, treatment).

7. *Surgery of the lungs, heart, and large blood vessels* (plastic surgery of the heart valves; use of heart-lung machine; application of hypothermia and hibernation for surgery; prophylaxis and treatment of fibrillation during cardiac surgery; surgical treatment of coronary insufficiency; peripheral vessel surgery; surgery of upper gastrointestinal tract).

8. *Surgery of the nervous system* (trauma of the central nervous system (CNS); diagnosis and surgical treatment of focal injuries; reaction of the brain in focal injuries).

9. *Pathogenesis, prophylaxis, and treatment of common diseases of the nervous system* (vascular and infectious diseases of the CNS, especially viral; diseases of the peripheral nervous system; neuroses).

10. *Malignant tumors* (etiology, pathogenesis, diagnosis and treatment,

including role of viruses; immunity to cancer; role of penetrating radiation in development of tumors; role of CNS and hormonal disorders in pathogenesis of tumors).

11. *Etiology, prophylaxis, and treatment of tuberculosis* (pathogenesis, clinical aspects, epidemiology).

12. *Epidemiology, prophylaxis, and treatment of intestinal infections, particularly dysentery* (pathophysiology of dysentery and acute intestinal disorders; etiology, epidemiology, clinical aspects, and treatment of dysentery and of acute intestinal infections generally).

13. *Health of women, mothers, and newborn children* (effect of cardiovascular disorders on the course and outcome of pregnancy, childbirth, and puerperal period; toxemias; regulation of labor; neonatal health; functional disease of female reproductive organs—climacteric and aging; radiation disease and gynecology; contraceptives and measures to increase the birth rate).

14. *Etiology, epidemiology, prophylaxis, and treatment of acute infections of childhood* (pathogenesis, immunity, active immunization, particularly in measles, scarlet fever, diphtheria, and pertussis).

15. *Physiological basis of rational nutrition for healthy and ill persons* (nutrition standards; prophylactic nutrition problems, especially in installations employing atomic energy and radioactive substances; role of individual foods in metabolism; low calorie-high nutrition diets; effects of residual poisonous chemicals used in agriculture; therapeutic nutrition).

16. *Labor hygiene and the prophylaxis of occupational diseases* (labor hygiene in industry and agriculture; occupational pathology of dust-producing operations and other specific factors in industrial environment; prophylaxis of industrial intoxications; effect of residual radioactivity in populated places and industrial installations).

17. *Hygiene of populated places* (acclimatization in the newly colonized regions of the USSR; standards for sanitary protection of air over populated places; quality and protection of drinking water; design and construction of residential and public buildings).

18. *Variability of microbes and its significance in biology and medicine* (the mechanism of variability leading to genus development; definition of the concept of microbial species; microbial metabolism; variability of bacteria and viruses during the epidemic process; virulent and avirulent vaccinal strains; directed variation in antigenic composition of regenerated filtrable forms; mechanisms of drug action; prevention of drug resistance).

19. *Etiology, epidemiology, and immunology of viral infections, particularly influenza* (general virology—physiology, pathogenesis and immunogenesis, prophylaxis, antibiotics and chemotherapy against viruses; practical aspects—probelms of infectious hepatitis, measles, live-virus vaccine, rabies, trachoma, and conjunctivitis; influenza—all aspects including serotherapy, seroprophylaxis, and live-virus vaccine).

20. *New antibiotics and synthetic chemotherapeutic agents* (synthesis

and production; mechanism of action; biological models of disease suitable for primary selection of antibiotics and synthetic drugs).

21. *Epidemic poliomyelitis* (killed and live-virus vaccines; laboratory diagnosis; etiology and epidemiology of poliomyelitis and polio-like diseases; clinical aspects and pathomorphology).

22. *Pediatrics* (anatomico-physiological features of growth and development; nutrition of infants and older children; hygiene and education of infants and older children; pathology of childhood—acute infections, especially intestinal, neuropsychiatric diseases of childhood, tuberculosis, rheumatic fever, poliomyelitis, respiratory diseases, hematologic disorders including leukemias).

The body of the document consists of careful elucidation of the objectives and approach to the specific problems. Many of the proposed studies apparently were in progress in 1955 or earlier as is evident from a summary of selected results of research projects sponsored by the Academy of Medical Sciences, USSR. The report was prepared for the Academy by M. A. Zhukovskii in July, 1956 and was published in December, 1956 (6). Its complete translation follows with some editorial and stylistic changes in conformance with the American writing habits.[3] Unfortunately, the publication lacks a bibliography but at the time it was written much of the work discussed had not yet been reported and it was not until 1957 that some of the reports were seeing print. In a few instances, when references to related publications by the same authors were known to us, these were separately listed.

The translated summary of selected recent advances, together with the recommendations of the current five-year plan, may familiarize the reader with the trends in Soviet medicine today and the names of the institutes and workers in his field of interest. This should ease the task of searching for significant contributions in the translated Russian journals and abstracts available in our libraries.

RESULTS OF SOME OF THE SCIENTIFIC PROJECTS SPONSORED DURING 1955 BY THE ACADEMY OF MEDICAL SCIENCES, USSR

By M. A. Zhukovskii,[4] Candidate of Medical Sciences

The Presidium of the Academy of Medical Sciences, USSR, yearly summarizes the results of scientific research activities of the component

[3] Sometimes exact equivalents of the less common Russian technical terms could not be ascertained, necessitating their direct translation or, in the case of derivatives coined by the Russians from Greco-Roman roots, direct transliteration.

[4] For the benefit of readers unfamiliar with Russian names a note of explanation might be of interest. The four common endings of Russian family names given in

Institutes of the Academy and selects the accomplishments which should be incorporated into the practice of preventive medicine. During 1955 the activities of the Academy of Medical Sciences included 23 particularly important problems to be recorded here.

Within the past three years the Ministry of Public Health prepared two directives to assure practical utilization of some of the recent advances and to give concrete instructions to the various divisions on how this can be accomplished. Many of the recommendations have been successfully followed in practice, but this is not always achieved smoothly as it depends to a considerable extent not only on the activities of the Ministry of Public Health itself but on its subdivisions as well.

One of the important advances was the broadened search for new antibiotics and chemotherapeutic preparations. Thus, the Antibiotic Research Institute (Director, Doct. Med. S. D. Iudintsev) in 1956 developed and tested under production conditions a new antibiotic, colimycin (belonging to the group of the neomycins). The drug was tested in the dermatological and surgical clinics in treatment of pyodermias and wound infections caused by *P. vulgaris* and *B. pyocyaneus* with good therapeutic results. Extended clinical application of colimycin is now in progress. A new antibiotic, heliomycin, with marked antiviral activity was found to be clinically effective in such infections as trachoma. It is being further tested in the Institute of Eye Diseases imeni Helmholtz.

Production methods on large laboratory scale were developed for a new antibiotic, actinoidin. At present its marked effect on the Gram-positive flora (mainly staphylococcus and streptococcus) is being studied and clinical application of the therapeutic forms is in progress. Application of actinoidin by aerosol inhalation is under study in the Institute of Pediatrics.

The Antibiotic Research Institute prepared a monograph, *Problems of Classification of Actinomycetes Antagonists,* which is now in print. This monograph should considerably facilitate the task of finding derivatives of new antibiotics.

The Institute of Pharmacology, Experimental Chemotherapy, and Chemoprophylaxis continued its investigations on synthesis of new therapeutic preparations. A pilot procedure for industrial production of an important antibiotic, tetracycline (cyclomycine) by means of catalytic dehalogenation of biomycin was developed and formulated. This is a new method, simpler than the usual technique of tetracycline production. Because the necessity

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the masculine form as *-ov, -ev, -in, -skii* are modified in the following fashion to indicate the feminine sex of the bearer: Korsakov—Korsakova, Prokofiev—Prokofieva, Borodin—Borodina, and Chaikovskii—Chaikovskaia. However, with certain less common endings and derived names the name is not changed, e.g., Shostakovich, Khachaturian, and so forth. Russian scientific institutes commonly are named after scientists prominent in the particular field. The word "imeni" stands for "in the name of."

for using organic solvents has been avoided, antibiotic extraction is simplified, potential explosiveness of the process due to the pyrophosphoric catalyst is decreased, and higher yields of the antibiotic are obtained. Clinical tests have so far shown that tetracycline possesses a number of advantages over currently used biomycin and reomycin. This study was performed by A. P. Arendaruk, L. A. Slonov, and T. V. Golovkina under the direction of A. P. Skoldinov.

In the same Institute, under the direction of Professor V. V. Zakusov and D. A. Kharkevich, N. F. Kucherova studied certain derivatives of carboline, which she had synthesized. She demonstrated experimentally that the most active antihistaminic and antianaphylactic preparation is a compound named diazolin (naphthalene-1,5-disulphonate-9-benzyl-*N*-methyl 1, 2, 3, 4-tetrahydrocarboline). Diazolin not only prevents histamine and anaphylactic shock but also counteracts acute bronchospasm and histamine effects on blood pressure as well as on the isolated ileum and uterine muscle preparations. Valuable properties of diazolin include its prolonged action and lack of depressive effect on the central nervous system, thus setting it apart from many other antihistaminic drugs and making it especially useful for ambulatory treatment of individuals whose work demands concentration. The negligible toxicity of this drug, its broad therapeutic spectrum, absence of an effect on the hematological picture, or on the liver function and cardiac activity, resulted in its recommendation by the Pharmacological Committee of the Ministry of Public Health for now current clinical testing in various allergic conditions.

The same Institute formulated a laboratory method for producing 5-6-dimethylbenzimidazole (a precursor of vitamin B_{12}). It was established that addition of this compound to the fermentation medium during biosynthesis of vitamin B_{12} was effective in increasing the yield several fold. The studies were performed by N. V. Smirnova, under A. P. Skoldinov's direction.

The synthesis of chloracon was accomplished in Professor N. K. Kochetkov's laboratory through interaction of appropriate substituted benzylamines with the chloranhydride of chlorpropionic acid. A general method of synthesis of basic substituted benzolamines from appropriate benzylchlorides through the uratropine salts was developed. Studies on the dependence of anticonvulsive effect on drug structure led to chloracon being selected as the most effective and easily produced drug and it is now being tested clinically. Antihistaminic drugs of the carboline series, tetrahydrocarbolines, have also been produced under the direction of N. K. Kochetkov, and their clinical antihistaminic activity is under investigation.

V. A. Mikhalev's group accomplished synthesis of biogenic arylethanolamines; the laboratory procedure is being applied industrially for producing a new synthetic sympathomimetic drug mezaton. A new laboratory method of sympathol production has also been developed. Comparative pharmacological investigations of a series of synthesized arylethanolamines have un-

covered new and interesting facts of antagonism between oxyphenyalkylamines of the epinephrine type and their structural analogues which contain nitro-groups instead of oxy-groups.

The Institute of Biological and Medical Chemistry developed a method of production of *dl* asparagine which has been used under factory conditions. Industrial production of this compound is planned after the necessary equipment is obtained. The Institute also released for industrial production detailed methods for synthesis of tagged amino acids as well as the key compounds necessary for their synthesis (7 amino acids tagged with carbon, and 11 amino acids tagged with heavy nitrogen). A method for production of crystalline pepsin was developed and released for industrial use.

Professor S. V. Anichkov's group of the Institute of Experimental Medicine synthesized a compound named hexonium, a gangliolytic, hypotensive preparation highly effective in therapy of experimental hypertension and experimental gastric ulcer. Another new drug, paramion, which possesses curare-like action was successfully synthesized. The Pharmacological Committee of the Ministry of Public Health released this drug for wide usage and the regulations governing its manufacture have been prepared.

In the Institute of Normal and Pathological Physiology, under the direction of Professor V. N. Chernigovskii, a series of investigations was conducted on (*a*) the functional interrelations between the receptor fields of internal organs and the various vascular fields of the organism, and (*b*) representation of internal organs in the cerebral cortex centers. Studies on the effect of stimulation or inhibition of entero-receptor fields on the vasomotor center have been completed. A method for registration of evoked potentials of cerebral cortex has been developed.

Professor M. E. Marshak's laboratory obtained new data on the role of phrenic nerves in the regulation of external respiration and blood circulation, establishing that instead of two afferent pathways three such pathways actually exist. A method for registration of coronary circulation in dogs in chronic experiments was perfected by G. N. Aronova. Data have been obtained on the qualitative contribution of cerebral cortex analyzers to the electrical reaction and on the changes in the rhythm of the conditioned auditory stimulus. This may aid in evaluating the specificity of the stimulus in studies of the electroencephalographic changes during conditioned reflex activity.

M. A. Sobakin developed an electrogastrographic method, combined with roentgenoscopy, for studying the physiological mechanisms regulating motor and secretory activity of the stomach. These electrogastrographic studies are based on a technique of recording on a specially constructed apparatus, the gastric bioelectric currents directly from the body surface, thus eliminating the necessity for catheterization. Several medical and surgical clinics demonstrated the possibility of using this method for studying the nonspecific alterations in digestive peristalsis in ulcerative and malignant disease of the stomach.

Doct. Med. D. F. Pletsity directed a study on the dependence of immunologic reactivity and resistance on the typological pecularities of the nervous system. He has also studied a rapid method of immunization against tetanus establishing that different immunization schedules are required for animals representative of the various types of higher nervous activity, as their immunogenesis apparently develops in different ways. His observations also show that tetanus toxoid appears in the bloodstream of vaccinated individuals sooner upon intramuscular rather than subcutaneous injection and is retained for a much longer period of time.

In the Laboratory of Experimental Physiology on Restoration of Life, a group of staff members directed by V. A. Negovskii, increased the resistance of the central nervous system to the effects of anemia by using artificial hypothermia. Experimental application of artificial cooling prolonged the period of clinical death to 60 min. with subsequent complete and stable re-establishment of vital functions. In the same laboratory, A. M. Gurvich conducted a study in dogs on the dynamics of cerebral cortex biopotentials during protracted periods of clinical dying from gradual exsanguination and during subsequent periods of recovery. It was found that the general character of electroencephalographic changes is similar whatever the duration of the experimental antemortem period, but the various phases of the process were more clearly distinguishable in experiments employing protracted exsanguination. The dynamics of restoration of cortical bioelectric currents following hemorrhage of many hours' duration is markedly different from that observed during re-establishment of vital functions with resuscitation begun after clinical death. It can be supposed that the mechanisms of functional restoration of the cerebral cortex are quite different in the two cases. The experimental data also suggest that the animal organism tolerates brief hemorrhage at a lower pressure better than many hours of progressive bleeding at a higher pressure. Electroencephalographic investigations during recovery from prolonged but incomplete loss of blood continued only to the point of development of terminal pause, or the onset of agony, provided evidence on reversibility of the functional changes in the cerebral cortex.

A group of staff members again directed by Professor V. A. Negovskii conducted a study on the application of complex methods of restoration of life in clinical treatment of certain terminal conditions. Observations made in a number of Moscow clinics show that in the extreme stages of shock certain terminal states are regularly observed representing markedly lowered and modified reactivity of the human organism. Hence, the fourth stage of torpid shock should be treated first with intra-arterial blood followed by its intravenous infusion. Only then morphine compounds, procaine blocks of certain zones, intravenous injections of procaine, or strongly acting and stimulating drugs should be given. Application of these measures prior to correction of decompensated circulation by means of arterial blood injection in most cases leads to further depression and accelerates breaking down of the exhausted compensatory mechanisms. Correct and

timely application of arterial blood transfusion in extreme stages of shock lowers the mortality by approximately 50 per cent. Several phases comprising the usually terminal states developing during cardiac surgery have been defined. Similar terminal phases in various forms of cardiac disease and the value of intra-arterial blood transfusions in their treatment have also been demonstrated.

In 1955, an apparatus for artificial respiration named "Gornospasatel-2" passed final laboratory and clinical tests and was approved by the Scientific Council of the Ministry of Health for mass production. Another machine named "AID" is now in mass production following laboratory and clinical tests.

The Brain Institute developed a new method of chemoarchitectonic analysis of intact preparations which permits studies on the distribution of enzymes and other biologically active substances within the macroscopic formations of the brain. By introducing a quantitative element this method permits comparative characterization of the level of enzymatic processes occurring in the various formations of the central nervous system or of its composition with respect to certain other substances. Brain slices 3 to 8 mm. thick are subjected to histochemical analysis; after appropriate histochemical reactions to facilitate isolation of enzymes or other substances, the brain slices are embedded in agar, according to Talalaev's method, and photographed; the negative images of the preparations are photometrically measured with the aid of a microphotometer. Depending on the character of the substances detected the preparations can be preserved for as long as 1 to 6 months. The method was developed in the Laboratory of Histochemistry by Professor V. V. Portugalov and V. A. Iakovlev.

Also at the Brain Institute G. I. Poliakov developed a new method of neuronocytoarchitectonic analysis (a method of colored cytoarchitectonic maps) which permits precise determination of qualitative and quantitative composition of the cerebral cortex neurons. This method makes it possible to measure exactly the quantitative and qualitative characteristics of the cellular structure of each individual cortical field.

In the Institute of Experimental Medicine under the direction of Academician N. N. Anichkov, it has been established that it is possible to compensate for impaired nutrition of the cardiac muscle in coronary arteriosclerosis through development of collateral circulation. A model of arteriosclerotic disease was produced and studied in dogs. Under Professor A. V. Rikkl's direction, a method was designed for manufacturing a dry preparation of natural gastric juice which does not lose its physiological properties upon prolonged storage.

In the same Institute, Professor V. I. Ioffe conducted microbiological and immunological evaluation of a method of treatment of scarlet fever with a therapeutic course of penicillin. It was established that this method leads to an increased incidence of recrudescences. To eliminate this he suggested the use of so-called "stimulatory immunization." Side reactions

of pertussis vaccines have been characterized and the dependence of these undesirable effects on the various components of the microbial cell has also been described. The results may aid in developing a method for experimental determination of side reactions likely to occur with antipertussis preparations.

Under the direction of Professor A. A. Smorodintsev, the effectiveness of anti-influenzal therapeutic serum was evaluated. The data from a number of clinics in Moscow, Kiev, and Leningrad, establish the high effectiveness of serotherapy when used early in the epidemic outbreaks due to influenza virus types A, A-prime, and B. A recent technological development insures the manufacture of stable and specific diagnostic influenza reagents for detection of not only virus-neutralizing but also complement-fixing antibodies in test sera. The method was accepted by the Vaccino-Serologic Commission of the Scientific Council of the Ministry of Health and has been assigned to the Leningrad Institute of Vaccines and Sera for mass production.

Experimental production of so-called "paper antigens" was studied in the Institute of Experimental Biology, under the direction of Professor V. S. Gostev. A paper antigen was prepared consisting of azoproteins firmly adsorbed onto paper, cotton fabric, and cotton. Fixation of the proteins on these materials was achieved by the introduction into the protein molecule of a chemical group which increased the sorbtive properties of protein many fold. Proteins fixed to paper or other fabric become insoluble and possess specific reactivity toward the appropriate antiserum. Utilization of this new form of insoluble antigen led to the discovery of new serologic reactions. It was found that the complement is specifically fixed on the surface of paper antigen in the presence of appropriate antiserum. A method for quantitative evaluation of this reaction has been developed by N. A. Shagunova who showed that the quantity of the adsorbed antigen used can be easily measured by weighing of the paper antigen. A new serological reaction of specific fixation of nitrogen onto paper antigen has been worked out (Shagunova, Grigorian). It was established that antigens fixed onto cotton, paper, and cotton fabric can specifically extract antibodies of definite quality from the antiserum. Paper antigens can be recommended for use with monospecific sera needed in clinical or experimental work.

The Institute of Epidemiology and Microbiology imeni N. F. Gamaleia, summarized the promising results of studies on a method of treating dysentery by antibiotics in combination with immunogens, conducted under the direction of Professor V. L. Troitskii in a number of clinics and therapeutic institutions of the country. The Ministry of Public Health recommends this method of treatment for patients with chronic dystentery.

Professor G. V. Vygodchikov's laboratory developed a method for purification of antigangrene toxoid yielding a preparation of high purity and concentration. Rational schemas of immunization and revaccination against tetanus and gas gangrene with purified concentrated gangrene and tetanus

toxoids (trianatoxin) have also been prepared. Under the direction of A. V. Beilinson a new apparatus for drying antitoxic sera in large quantities was designed and introduced into serum production. Professor L. A. Zil'ber supervised three clinics in the expansion of their studies of the anticancer vaccine as a means of prevention of relapses in cancer patients.

Using new techniques of depth cultivation, a method was developed for regularly rapid (48 to 60 hr.) production of diphtheria toxin (P. V. Pavlov, A. G. Leonova, E. I. Nekhotenova, and others).

Professor P. F. Zdrodovskii directed experimental work on a simple method of allergenic diagnosis of Q fever by means of intracutaneous tests which will probably lead to improved sero-diagnosis of this disease. A vaccine against Q fever was developed, tested, and directions for its manufacture, control, and application have been transmitted for utilization in practice.

In collaboration with clinicians, a project was completed on a precipitation reaction of patients' urine with antistreptococcal typing sera for diagnosis of scarlatinal and other streptococcal infections. Clinical results confirm the diagnostic value of this method and provide a basis for its practical application not only in diagnosis of abortive forms of scarlet fever but also for determination of the infectiousness of convalescent carriers (I. N. Liampert). Studies are in progress on the effectiveness of live vaccine against brucellosis, specifically, the vaccine prepared from strain VA. Methods of preparation of live vaccine against tuberculosis have been improved and the effectiveness of this vaccine has been established (Professor P. A. Vershilova).

The Institute of Virology submitted for practical utilization a method for preparation of dry and liquid diagnostic influenza reagents intended for use in hemagglutination-inhibition and complement-fixation reactions. A check on the quality of these preparations conducted in a number of institutes of epidemiology and microbiology by G. V. Eremeyev disclosed that the dry as well as the liquid diagnostic reagents remain stable for a considerable period of time: the antigen did not change its activity during a year's storage at temperatures of +4 to +10°C. and retained its specificity, permitting serological differentiation between Japanese encephalitis, tick typhus, brucellosis, and other diseases.

The Institute of Neurology presented new data on the respiratory disturbances in poliomyelitis. Indications and contraindications for the use of mechanical artificial respiration in poliomyelitis were determined and the methods of respirator treatment were worked out in detail. L. M. Pavlova, G. R. Buravtseva, and others conducted tests on numerous respirator models of national as well as of foreign manufacture. In collaboration with the Laboratory of Experimental Physiology for Restoration of Life, a new tracheotomy tube for intratracheal artificial respiration was designed and tried.

The Institute of Neurology studied the possibility of using electromyography for topical diagnosis and determination of the severity of pathological processes as well as detection of subtle lesions of the central nervous system. New techniques have been worked out for electromyographic tests in diagnosis of abortive and atypical forms of acute poliomyelitis. These methods should also be helpful in differential diagnosis of organic and functional speech disturbances.

The same Institute tested new drugs named tropatzin and aminazin used for treatment of spastic paralyses of vascular origin. Their effectiveness in diminishing spastic phenomena was demonstrated and methods for their use were developed (Professor L. G. Chlenov and M. P. Serova).

L. I. Aleksandrova delineated indications and contraindications for therapy with sleep in functional diseases of the nervous system. On the basis of her study a document was prepared entitled, "Statement on the Use of Sleep Therapy in Treatment of Neuroses," which has been approved by the Scientific Council of the Ministry of Public Health.

In the Institute for Tuberculosis further improved methods of combined prolonged patient therapy with antibacterial drugs were developed on the basis of clinical and microscopic studies. A method of early treatment of patients with initial stages of primary tuberculous infection was described and applied in practice.

Contrary to the statements made in the foreign literature, treatment of a certain group of tuberculous patients with ACTH in combination with antibacterial drugs (according to the principle of combined etiotropic and pathogenetic therapy) was found to be successful. Studies conducted by the outpatient section of the Institute of Tuberculosis and the combined data from several cities confirm the effectiveness of antituberculosis measures designed to diminish the morbidity and mortality from this disease. Experimental studies of a new vaccinogenic strain of *Mycobacterium tuberculosis* were concluded and it was experimentally used in combination with BCG in order to enhance the immunizing properties of the BCG vaccine.

In the Institute of Experimental Pathology and Cancer Therapy, new antitumor drugs named sarcolysin and dopan have been synthesized. Experimental testing of these drugs indicates their effectiveness against some malignant neoplasms.

The Institute of Oncology demonstrated that tissue culture methods can be utilized for studies on the viral nature of human neoplasms and the possibility of eventual utilization of these methods in everyday practice is being considered.

The same Institute established the presence of a carcinogenic substance 3, 4-benzpyrene in the atmospheric air over several cities in the Donbass area, as well as in the soot of certain fish-smoking industries of Latvia, and in the by-products of artificial liquid fuel manufacture. P. P. Dikun studied the possible blastomogenic action of the by-products of manufacturing arti-

ficial liquid fuel. The data obtained became the basis for formulation of appropriate prophylactic measures. Under the direction of A. V. Chaklin a valuable statistical analysis was made of the clinical data collected by the Institute from 1926 to 1952, and of the five-year therapeutic results in patients with the more common forms of malignant tumors.

Professor B. G. Egorov's group in the Institute of Neurosurgery conducted interesting studies on the anatomico-physiological aspects of neurosurgical operations for neuroectodermal frontal lobe tumors. These studies demonstrated that in attacking the intracranial tumors through the frontal lobe, even when they are located in the posterior portions of the lobe, the most sparing approach is through the superior frontal convolution or through the mid-portion of the mid-frontal convolution with separation of the white brain matter in the sagittal plane. V. E. Maiorchik and M. A. Nikitin, working with Professor B. G. Egorov, developed a technique for recording the electrocorticogram during surgery. The electrocorticogram helps to characterize the functional state of the cortex in the area of the pathological focus and to localize the tumor more precisely. Simultaneous registration of the electrocorticogram, electroencephalogram, electrocardiogram, and pneumogram makes it possible to evaluate objectively local and general reactions of the brain, and also the changes in the cardiovascular and respiratory activity, in response to various stimuli, including the onset of necrosis.

Professor A. A. Arendt and S. I. Kuznetsova studied pathologic aspects of cerebrospinal fluid circulation during prolonged drainage of the ventricular system. It was found that a technique of drainage of the lateral ventricles definitely is of practical value in treatment of brain tumors associated with development of hydrocephalus. The abolition of acute cerebral hypertension with return of intracranial pressure to normal favors surgery under more optimal conditions.

The Institute of Surgery imeni A. V. Vishnevskii described a technique of local anesthesia in surgery for mitral stenosis. The commissurotomy procedure under local anesthesia was first developed in 1954 and applied in 50 cases during 1955. This technique can be highly recommended in cardiac surgery.

The same Institute attempted to clarify the problem of activity of the rheumatic process. Biopsies of the auricular appendage, resected during operations for mitral stenosis, supplied information as to the presence of silently active rheumatic processes in the patient, thus aiding in correct postoperative regimen and institution of appropriate antirheumatic therapy. A number of new operative procedures for congenital cardiac disorders, and specifically the Blalock operation for cyanotic heart disease, have been performed. It is known that this particular operation is associated with failures in 30 per cent of the cases resulting from inadvertent stretching of the subclavian artery. Lengthening the subclavian artery by means of a vascular

transplant, which has been previously preserved at low temperature under vacuum combined with the use of rings developed by D. A. Donetskii, makes it possible to avoid this serious complication. In the same Institute, N. K. Galankin and T. M. Darvinian developed an operation for caval-pulmonary-arterial anastomosis in dog surgery experiments.

During 1955 the Institute used vascular homotransplants in the therapy of patients with aneurysms and congenital heart disease. Technical directions of preparation and application of homotransplants have been prepared and transmitted to the Scientific Council of the Ministry of Public Health.

Professor P. K. Anokhin continued his studies of the compensation process which takes place following surgery on the lung. Specifically, the stability of the compensatory adaptation of the cardiovascular system following pneumonectomy in relation to increased load of physical work, stress of hydration, and of temperature were investigated, with results to be utilized for proper postoperative regimen. Necessity for oxygen administration during chest surgery was demonstrated experimentally. Completed studies of gaseous exchange and external respiration in patients with lung disease when subjected to moderate stress before and after surgery may have prognostic significance.

The Institute of Surgery together with the Moscow Municipal Orthopedic Hospital conducted experimental studies in rabbits on grafting of homogenous bone transplants preserved by cold. Following experimental studies frozen homogenous bone transplants were successfully used for a number of hospitalized patients. The data warrant recommending the use of such homotransplants when autotransplants are not available.

Studies were also conducted on the effect of hypothermia and of certain ganglioblocking agents on the individual functions of the organism under experiment.

The effect of aminazin on the duration of procaine anesthesia was examined. Apparently aminazin prolongs the action of procaine and this effect is more marked upon local application of aminazin in combination with procaine rather than during its general action on the organism.

Professor A. I. Dobrokhotova's group of the Institute of Pediatrics continued the study of pathogenesis of pertussis and conducted comparative evaluation of the effectiveness of various methods of treatment and prophylaxis, especially the pertussis vaccine.

Professor B. N. Klosovskii was responsible for the development of a method of total inhibition of visual, auditory, vestibular, and olfactory receptors. V. R. Purin contributed a method of continued measurement of intracranial pressure in animals. N. S. Volzhina and V. R. Purin developed a thermoelectric method for studies on cerebrospinal fluid production within the intact skull. A. M. Fonarev presented a method of registration of blinking reflexes in nursing infants and proposed an apparatus for its registration using a photoelectric cell. He also constructed a special chamber

(camera)[5] for studies of the higher nervous activity in children.

Professor O. D. Sokolova-Ponomareva directed studies on the clinical aspects and pathogenesis of rheumatic fever. Studies on the status of higher nervous activity in rheumatic fever (A. V. Galaktionova) and on the therapy of chorea by means of prolonged sleep (E. A. Blei) have been completed. A method for aerosol inhalation of antibiotics for treatment of patients with chronic tonsillitis, with determinations of antibiotic sensitivity of the individual throat flora, was described.

The Institute of Nutrition studied nutrient values of more than 160 samples of foreign baby foods and the desirable items were selected for production in the Soviet Union. The same Institute, jointly with the Professional Institutes of Food Industry, developed recipes and technologic aspects of preparation of more than 50 foods. Studies on nutrition of patients with coronary insufficiency disclosed that regularly scheduled ingestion of food during the day plays an important role in proper convalescence; ingestion of large quantities of food may lead to unfavorable changes in the electrocardiogram and affect the patient's sense of well-being. The effects of certain vitamins on blood coagulation were investigated, showing that ascorbic acid does not have any effect on blood clotting while nicotinic acid, which is used occasionally by clinicians in large doses, increases the coagulability of blood.

On assignment from the Committee on Salaries of the Council of Ministers, the Institute reported their physiologic evaluation of the nutritional problems of the low income laborers and other employees in three different geographic zones of the USSR (North, South, and Central), and worked out the minimum food rations for these population groups. The report was utilized by the Committee on Salaries in determining the minimal rates of pay in various zones of the USSR and in the Soviet Union as a whole. On assignment from the Gosplan (Government Planning Commission), the Institute also worked out the minimal standards for various food products in accordance with basic physiological requirements as a step toward complete realization of scientifically determined nutritional standards.

The Institute of Work Hygiene and Occupational Diseases studied the effects of working conditions on morbidity among electrical welders in shipyards. Certain concrete suggestions to improve their working conditions were proposed and submitted to the shipyards inspected and the Ministry of Shipbuilding. The Minister of Shipbuilding Industry, in his order of 11 August 1955 No. 596, entitled "On the Working Conditions in Electrical Welding Jobs and Measures to Improve Such Conditions," foresees utilization of health measures developed by the Institute of Work Hygiene and the Leningrad Institute of Industrial Safety. This work was conducted under the direction of E. I. Vorontsova.

[5] The Russian use of the word camera may mean either "chamber" or "photographic camera."

In response to an inquiry from the Ministry of Commerce, studies have been conducted on health aspects of working in the refrigerating industry. Close analysis of various illnesses, resulting in temporary inability to work, disclosed considerable morbidity among employees of refrigerating industry with the highest absenteeism being due to common cold-like illnesses and diseases of the peripheral nervous system. The Institute recommended a number of measures to improve the working conditions. Most of these measures have now been accepted by the Ministry of Commerce and are being put into practice.

The Institute of General and Communal Hygiene produced sanitary regulations for planning, building, and public welfare of populated rural areas (Kolkhozs, MTS Estates, and Sovkhos). These regulations have been approved by the Chief Sanitary Inspector of the USSR and have been issued as directives for practical sanitary control. A statement has been composed giving directives for the determination of dust content and bacterial contamination of atmospheric air over the cities. A new method was developed for determining free silicon dioxide in atmospheric dust and in industrial wastes. This rapid method (1-1½ hr. instead of 1-1½ days) does not require expensive equipment. The Institute tested and approved a haptene-precipitation method for bacteriological water analysis for pathogenic bacteria (typhoid, paratyphoid, and dysentery). Sanitary regulations were worked out for building of improved, light weight, prefabricated homes intended for supplying the newly colonized areas. These regulations have been approved by the Chief Sanitary Inspector's Office of the USSR and sent to the proper building management offices. Various types and systems of radiant heating were studied and the conclusions were transmitted for use in planning such heating systems in new housing construction.

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